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SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. MCKEEN CATTELL and published every Friday by

THE SCIENCE PRESS

New York City: Grand Central Terminal

Lancaster, Pa. Garrison, N. Y.

Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

SYNTHESIS AND DEGRADATION OF PROTEINS IN THE LABORATORY AND IN METABOLISM[1]

By MAX BERGMANN

KAISER WILHELM-INSTITUT FÜR LEDERFORSCHUNG IN DRESDEN

EVER since men have interested themselves in the study of the chemistry of vital processes the proteins have exercised a peculiar fascination. Many of our most distinguished investigators have been engaged in problems associated with their chemistry and metabolism. I need mention only such names as Dakin, Levene, Osborne and van Slyke among others in order to recall to your minds the achievements of modern protein chemistry in this country. Nevertheless, we are still far from an exact knowledge of the structure of a single protein molecule.

The foundations of our modern knowledge of proteins were laid for the most part by Emil Fischer and by Albrecht Kossel. These investigators provided the methods by which we separate and recognize the individual products resulting from the hydrolysis of proteins. To Fischer we owe the method of welding together the constituents of proteins by laboratory methods to form peptide structures resembling in character the proteins themselves. Fischer succeeded in synthesizing an octadecapeptide containing glycine and leucine. The latter striking synthetic achievement itself indicates, however, the unfortunate limitations of Fischer's methods, the application of which is confined almost exclusively to peptides containing the simplest amino-acids and the monoamino-monocarboxylic acids. Such peptides do not contain the free amino, carboxyl and guanidino groups, which are present in the natural proteins; they do not in fact contain the more complicated and therefore more interesting amino-acids.

If it is desired, therefore, to imitate the synthesis

[1] Lecture given November 17, 1933, in the Rockefeller Institute for Medical Research, New York.

of the natural proteins and thoroughly to explain the mode of action of the proteolytic enzymes it is evidently necessary to devise a method of synthesis which is more generally applicable than the classical method of Fischer. The search for such a synthesis has occupied chemists for a long time. My colleague, Dr. L. Zervas, and myself have recently been able to solve the problem in the following way.

The essential feature of this method is the nature of the residue which we use to block the amino group. This group must be of an acid nature, as its function consists in abolishing the basic properties of the amino group; moreover, it must be of such character as to be readily and completely removable from the amino group in the course of the synthesis, under conditions in which the rest of the molecule remains intact. Of the many substituents tried, the carbobenzoxy group proved the most suitable.

The free benzyl-carbonic acid (I) itself is unknown. But its acid chloride (II), readily obtainable by the interaction of benzyl-alcohol and phosgene, can be condensed with any amino-acid to yield the corresponding carbobenzoxy derivative (III). The carbobenzoxy amino-acids are beautifully crystalline substances which can be easily transformed into their acid chlorides (IV) or azides, and these in turn can be condensed with other amino-acids to yield carbobenzoxy peptides (V). Most important, however, is the fact that the carbobenzoxy residue can be split off without the employment of a hydrolytic agent, so that it can be eliminated from a carbobenzoxy peptide without danger of splitting the peptide bond. The removal of the carbobenzoxy residue is accomplished by catalytic hydrogenation in presence of palladium black, under which conditions the benzyl residue is eliminated as toluene and the resulting carboxy-amino derivative spontaneously loses carbon dioxide to give the free peptide (VI). The last step of the process proceeds with ease and in most cases almost quantitatively.

$C_7H_7 \cdot O \cdot CO \cdot OH$ (I)
$C_7H_7 \cdot O \cdot CO \cdot Cl$ (II)
$C_7H_7 \cdot O \cdot CO \cdot NH \cdot CH(R) \cdot COOH$ (III)
$C_7H_7 \cdot O \cdot CO \cdot NH \cdot CH(R) \cdot CO \cdot Cl$ (IV)
$C_7H_7 \cdot O \cdot CO \cdot NH \cdot CH(R) \cdot CO \cdot NH \cdot CH(R') \cdot COOH$ (V)
$C_7H_8 + CO_2 + NH_2 \cdot CH(R) \cdot CO \cdot NH \cdot CH(R') \cdot COOH$ (VI)

A further and very important advantage of the carbobenzoxy method is its applicability to optically active amino-acids. The carbobenzoxy-amino acids, in contrast to other acyl derivatives of amino-acids, are surprisingly stable towards racemizing influences. With the aid of the carbobenzoxy method, in fact, the preparation of many optically active peptides, which have hitherto been practically inaccessible, becomes a simple matter.

In presence of sulfur compounds like cystin the catalytic hydrogenation unfortunately does not work. For the synthesis of cystin-peptides another method of elimination of the carbobenzoxy residue is available.

There is only one amino-acid with which the benzylcarbonato method fails, and that is arginine; for the latter we have to devise a modified process. The difficulty in the case of arginine consists not only in the presence of more than one basic group, but particularly in the very strongly basic nature of the guanidino group, which masks the acid character of the carboxyl. In some instances it is impossible to alter the carboxyl group without simultaneously affecting the guanidino group. In order to render arginine suitable for the synthesis of peptides it was therefore necessary to neutralize its basic properties by a readily removable acid group. To this end we have modified the application of the carbobenzoxy method to arginine by first converting the latter into nitroarginine; the latter compound behaves like a simple monoamino-acid. The process may be illustrated by an example. For the synthesis of glycyl-l-arginine, carbobenzoxy glycine chloride is coupled with nitroarginine (VII) and the product (VIII) is subjected to catalytic hydrogenation; by this means the carbobenzoxy residue and the nitro group are removed in one operation and glycyl-l-arginine (IX) results.

$NH \cdot C(=NH) \cdot NH \cdot (CH_2)_3 \cdot CH \cdot COOH$ (VII)
(NH bearing NO_2; CH bearing NH_2)

$NH \cdot C(=NH) \cdot NH \cdot (CH_2)_3 \cdot CH \cdot COOH$ (VIII)
(NH bearing NO_2; CH bearing $NH \cdot CO \cdot CH_2 \cdot NH \cdot CO \cdot O \cdot C_7H_7$)

$NH_2 \cdot C(=NH) \cdot NH \cdot (CH_2)_3 \cdot CH \cdot COOH$ (IX)
(CH bearing $NH \cdot CO \cdot CH_2 \cdot NH_2$)

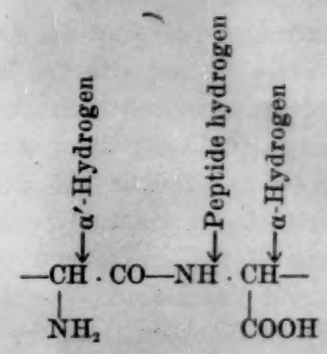
With the help of the carbobenzoxy method, it is now possible to bring into peptide combination aminodicarboxylic acids, diamino-acids, proline, cystine and serine, so that for the first time the different possibilities of combination of the amino-acids within the proteins and the behavior of the latter towards proteolytic enzymes can be accurately studied.

The following list contains a selection of dipeptides which we have been able to prepare during the past year by means of the carbobenzoxy method:

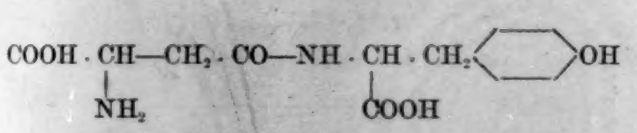
l-Glutamyl-l-glutamic acid
l-Lysyl-l-glutamic acid
l-Lysyl-l-aspartic acid
l-Lysyl-glycine
l-Lysyl-l-histidine
l-Glutamyl-l-tyrosine
l-Tyrosyl-l-tyrosine
l-Tyrosyl-l-aspartic acid
Glycyl-l-arginine

We have subjected all these dipeptides to the action of dipeptidase, in order to ascertain whether the effi-

cacy of the enzyme is influenced by the presence of free amino, guanidino, carboxyl or phenolic hydroxyl groups. This is not the case. All these dipeptides containing complex amino-acids are split by dipeptidase in precisely the same manner as the dipeptides of the simple amino-acids. We can therefore say with complete certainty *that every dipeptide containing natural α-amino-acids and normal peptide linkages will be hydrolyzed by dipeptidase.* In other words, dipeptidase is capable of hydrolyzing the peptide linkage so long as the latter is immediately adjacent to a free amino group on the one side and a free carboxyl on the other, according to the following scheme:

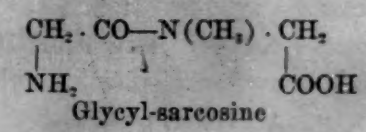


If the amino group or the carboxyl are further removed from the peptide linkage, as for instance in the case of β-l-asparagyl-l-tyrosine, the action of dipeptidase fails.

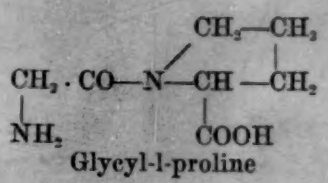


In order to obtain a deeper insight into the mechanism of the action of dipeptidase we have undertaken a series of further problems.

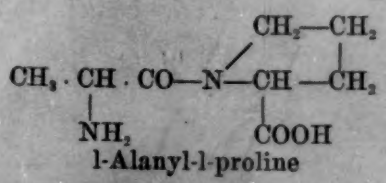
The first of these is the question whether the peptide hydrogen is of importance for the action of the enzyme. We have been able to obtain an answer to this question by investigating the action of dipeptidase on the following dipeptides:



Glycyl-sarcosine



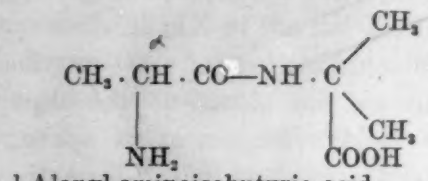
Glycyl-l-proline



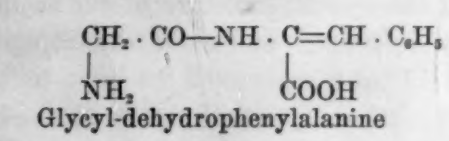
l-Alanyl-l-proline

These three dipeptides are all resistant to the action of dipeptidase. This has already been shown for glycyl-sarcosine by the earlier work of Levene and Simms[2] with erepsin. It appears, therefore, that *the presence of the peptide hydrogen atom is indispensable for the action of this enzyme.*

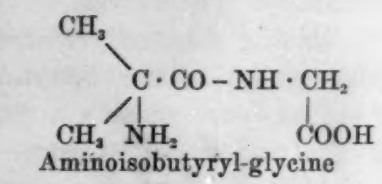
We next studied the question of the influence of the hydrogen atoms in the α- and α′-positions on the action of dipeptidase on dipeptides, such as:



l-Alanyl-aminoisobutyric acid



Glycyl-dehydrophenylalanine



Aminoisobutyryl-glycine

None of these peptides was attacked by dipeptidase, so that we can assume that *the hydrogen atoms in the α- and α′-position are important to the action of dipeptidase.*[3]

In order to restrict the field of our discussion still further we may recall the fact that dipeptidase only attacks those dipeptides which are built up from the natural optically active amino-acids, which, as is well known, all possess the same spatial configuration. The presence in a dipeptide of merely one amino-acid of the opposite configuration is sufficient to inhibit the action of dipeptidase. We can therefore add the statement that it is not sufficient that hydrogen atoms should be present in the α- and α′-positions; *these hydrogen atoms must occupy a definite position in the spatial configuration of the molecule.*

We have now been able to collect so many data that we are able to present an effective picture of the mechanism of the action of dipeptidase. When the enzyme combines with a dipeptide, the peptide linkage is rearranged into its imide form—

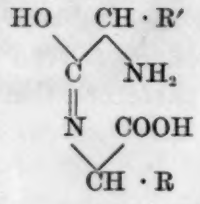
$$-C(OH)=N-$$

The imide form of the dipeptides can occur in two stereomeric arrangements X and XI.

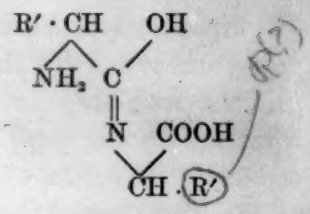
[2] *Jour. Biol. Chem.*, lxii: 711, 1925.

[3] P. A. Levene, R. E. Steiger and L. W. Bass (*Jour. Biol. Chem.*, lxxxii: 155, 1929) have shown that Glycyl-α-aminoisobutyric acid and Glycyl-d-l-phenylmethyl-aminoacetic acid are not split by erepsin. The same applies to Glycyl-d-isovaline and Glycyl-d-l-isovaline as has been shown by Levene and by myself.

X.

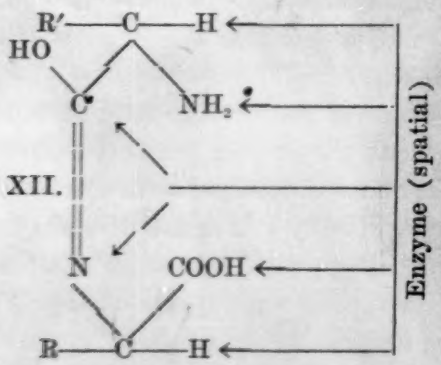


XI.



Of these, only X is attacked by dipeptidase, because the enzyme requires the simultaneous presence of a free carboxyl and a free amino group, which must exist (as in X but not in XI) in close spatial proximity. The combination of the enzyme with these groups forces the atoms of the dipeptide into a relatively rigid arrangement in space; the enzyme brings about a kind of "ring"-formation. In consequence of the spatial structure of the amino-acids the α- and α′-hydrogen atoms of the dipeptide lie on the same side of the plane of the peptide "ring." The enzyme can thus approach both of these hydrogen atoms simultaneously. The enzyme may therefore be regarded as combining chemically with at least three different atomic groups of the dipeptide, that is to say with the carboxyl, the amino group and the peptide linkage. The presence of hydrogen atoms in the α- and α′-positions, and in the correct spatial configuration, is also essential.

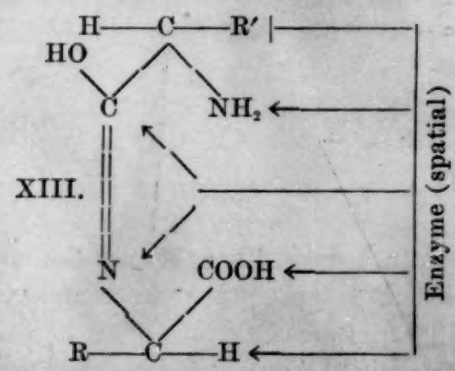
XII.



We can now understand why it is that glycine dipeptides are split by dipeptidase, although glycine contains no asymmetric carbon atoms; the reason is that the α-carbon atom of glycine carries two hydrogen atoms, one of which must always occupy the position required by the enzyme in accordance with the scheme which has been outlined.

Since the time of Emil Fischer the view has been generally accepted that the enzymes have specifically different spatial structures. It was in order to express this generalization that Fischer proposed his classical analogy of the lock and key. Now it becomes possible for us, as the result of our more recent investigations, to form a clearer idea of the reasons for the structural specificity of the enzyme dipeptidase. The enzyme itself must contain a whole series of chemically different atomic groups in a definite spatial arrangement; these groups must be so situated that they are capable of entering into combination with the carboxyl, the amino group and the peptide bond of the dipeptides. If the enzyme is brought into contact with a stereoisomeride of the natural peptide it finds the significant atomic groups of the dipeptide in an unsuitable arrangement; the active groups of the enzyme are unable to combine with all those of the dipeptide, and the latter therefore can not be split (XIII).

XIII.



Hitherto I have spoken of the way in which, with the help of the carbobenzoxy method it is possible to penetrate more deeply into the chemistry of the dipeptides and of their appropriate enzymes, the dipeptidases; this same method can however be used for the investigation of polypeptides and of the enzymes which hydrolyze them.

It is well known that polypeptides containing three or more amino-acids are not attacked by dipeptidase. The polypeptides have indeed their own appropriate enzymes, the polypeptidases; these are usually separated into two main groups: the carboxypolypeptidases, which attack the peptide from the carboxyl end by splitting off the amino-acid whose carboxyl group is free, and the amino-polypeptidases, which attack the polypeptide chain from the amino end.

First of all I should like to speak of the carboxypolypeptidase of the pancreas, and from the outset I must point out that this enzyme is not strictly entitled to the name of polypeptidase; its field of action is not limited to true polypeptides. It has been known, for instance, for some time past that this enzyme hydrolyzes chloracetyl-l-tyrosine (XIV) with especial ease; besides this we have found that it is also able to hydrolyze pyruvoyl-phenylalanine (XV) and that even genuine dipeptides, such as d-tyrosyl-l-arginine (XVI) and l-tyrosyl-l-tyrosine (XVII) are susceptible to its attack. It is thus possible to state that the substrate for the carboxy-polypeptidase must contain a free carboxyl group adjacent to the peptide linkage, but that the second peptide component of the substrate need possess not a hydrogen atom in α′-position. In this respect the polypeptidases differ fundamentally from dipeptidase. The presence of an amino group adjacent to the peptide linkage does not inhibit the action of polypeptidase in all cases, as is shown by the examples of tyrosyl-arginine and tyrosyl-tyrosine mentioned above. There are, however, only

a few dipeptides which are split by polypeptidase; the majority remain unattacked.

A simple experiment shows that carboxy-polypeptidase is unable to act in the absence of peptide hydrogen; whereas, as already mentioned, chloracetyl-l-tyrosine (XIV) is readily split by the enzyme, chloracetyl-l-methyltyrosine (XVIII) is quite resistant to its action.

XIV. $Cl \cdot CH_2 \cdot CO{-}NH \cdot CH(CH_2{-}C_6H_4{-}OH) \cdot COOH$

XV. $CH_3 \cdot CO \cdot CO{-}NH \cdot CH(CH_2{-}C_6H_5) \cdot COOH$

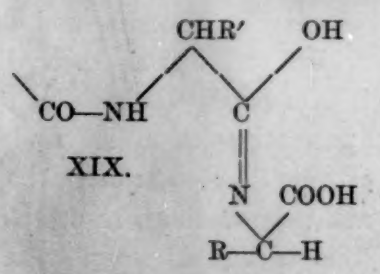
XVI. $HO{-}C_6H_4{-}CH_2 \cdot CH(NH_2) \cdot CO{-}NH \cdot CH((CH_2)_3 \cdot N_2CH_4) \cdot COOH$

XVII. $HO{-}C_6H_4{-}CH_2 \cdot CH(NH_2) \cdot CO{-}NH \cdot CH(CH_2{-}C_6H_4{-}OH) \cdot COOH$

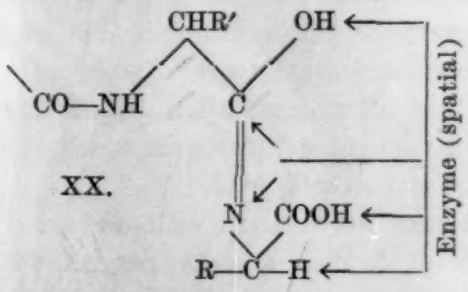
XVIII. $Cl \cdot CH_2 \cdot CO{-}N(CH_3) \cdot CH(CH_2{-}C_6H_4{-}OH) \cdot COOH$

The indispensability of the peptide hydrogen atom and of the free carboxyl group, as well as the inhibitive influence of a free amino group on the action of carboxy-polypeptidase lead to the following interpretation of its mode of action: The enzyme first combines with the peptide in its imide form (shown, for the case of polypeptides, by XIX); an intermediate molecular compound XX being produced.

XIX.



XX.



Only those dipeptides which, like tyrosylamino acids, can exist in the form represented by XI, are split by carboxypolypeptidase. On the other hand, dipeptides which assume the form X are not attacked by carboxypolypeptidase.

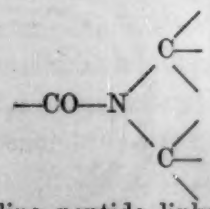
The same considerations hold good for the amino-polypeptidases. These are by no means limited in their action to true polypeptides; they split the amides of simple amino-acids and we have also found that they are able to hydrolyze certain dipeptides. Of the latter I may mention glycyl-l-proline and l-alanyl-l-proline.

This indicates that amino-polypeptidase does not require the presence of peptide hydrogen; its mode of action must be quite different from that of dipeptidase and carboxy-polypeptidase.

You will see that the possibility of the synthesis of selected peptides seems to open the way to an understanding of the action of these enzymes as complete as that which we already possess in the case of dipeptidase.

The higher we go, however, in the series of proteolytic enzymes the more restricted becomes our knowledge. I am thinking now of the so-called proteinases, that is to say, the enzymes which attack genuine proteins. To this class belong pepsin, trypsin, papain and kathepsin. We are almost entirely ignorant of the mode of action of these enzymes; it is the exploration of this very group, however, which is of the most fundamental significance for the elucidation of the structure of the genuine proteins. Are the proteins merely polypeptides with chains of enormous length, which are broken by the proteinases into smaller fragments, or may the protein molecule perhaps contain unrecognized linkages on which the proteinases exercise a specific action? We can not answer these questions because it has not yet been possible to obtain a single substrate of known structure on which to study the mode of action of proteinases.

The problem of proteinases and of the structure of the genuine proteins is of such outstanding importance that we have explored many different methods of attack. In the first place, we have attempted to obtain more precise information as to whether the proteinases are able to attack specific linkages in the protein molecule. One species of amino-acid is known to occur in protein which is not capable of entering into a normal peptide linkage, namely l-proline and l-hydroxy-proline, which in contrast with all other natural amino-acids contain no amino group but have their nitrogen in the imino condition. When proline is converted into a peptide through its nitrogen atom, therefore, no ordinary peptide linkage is formed but a linkage in which the nitrogen is in the tertiary condition.



proline peptide linkage

It seems to us of interest to find out whether such proline-peptide linkages occur in proteins and if so whether they are hydrolyzed by proteinases.

The ordinary method of following analytically the hydrolysis of the usual peptide linkage is accompanied by the liberation of one amino group and one carboxyl. The amino group can be estimated by the method of van Slyke, the carboxyl by titration in alcoholic solution according to Willstätter and Waldschmidt-Leitz. The analytical study of the digestion of proteins has as yet given no grounds for suspicion that amino and carboxyl groups can be liberated in any other proportion; this ratio has indeed been regarded as a criterion of true proteolysis.

Our synthetic proline peptides were the first examples of peptide compounds in which this law of equivalence was not fulfilled. In the process of hydrolysis of glycyl-prolines the carboxyl group of the glycine is liberated and can be titrated in alcoholic solution; simultaneously, the imino group of the proline is set free, but this group can not be determined by the method of van Slyke. In this case, therefore, the law of equivalence breaks down. We have been able to show that such proline-peptide linkages occur in gelatine and that they are not attacked by the pancreatic proteinase.

Gelatine contains about 25 per cent. of proline and hydroxy-proline. The process of digestion of gelatine, first by pancreatic proteinase and then by the enzymes of the intestinal mucosa has been investigated in detail. The digestion by the proteinase results in a rapid increase in the free amino and carboxyl groups, these free groups increase in equivalent proportions. During the second stage of the digestion with the intestinal enzymes the increase in free carboxyl groups predominates greatly over the increase in amino groups; this latter observation affords the first example of digestion of a protein in which the law of equivalence does not hold good.

Our experiments have provided us with the proof that large amounts of proline and hydroxyproline occur in the gelatine molecule linked through their nitrogen atoms, that is to say that the proline in gelatine is present for the most part in a linkage analogous to that of our synthetic proline peptides. On the other hand, our results also show without doubt that these proline peptide linkages are not hydrolyzed by pancreatic proteinase. It is therefore evident that the explanation of the mode of action of proteinase must be sought in another direction.

It has indeed been quite impossible up to the present to find any amino-acids, even of exceptional structure, simple derivatives of which are capable of acting as substrates for proteinases. We are, therefore, driven to the conclusion that it may perhaps only be the length of the peptide chain which decides its susceptibility to attack by these enzymes. It thus becomes one of the most important tasks of contemporary protein chemistry to synthesize polypeptides of large molecular weight and to investigate their behavior towards proteinases. Emil Fischer's octadecapeptide contains fifteen glycine residues and three leucine residues and is thus composed only of two different simple amino-acids; the peptides of glycine, which occurs fifteen times in the molecule, are well known to be particularly resistant to enzymic hydrolysis. It is, therefore, not surprising that polypeptides of the above type, in so far as their costliness has permitted them to be used for experiment, have shown themselves to be resistant to hydrolysis by proteinase.

In this matter the direction to be followed by further work is clearly indicated. The carbobenzoxy method provides the possibility of building up long polypeptide chains containing all the naturally occurring amino-acids. We are thus able now to offer the proteinases a substrate which resembles their natural substrate much more closely than did the simple polypeptides prepared by Fischer. We believe indeed that we may be able in the near future to express a definite opinion regarding the behavior of the proteinases towards peptide chains of high molecular weight and that we shall even be able definitely to sort out the modes of action of the different proteinases.

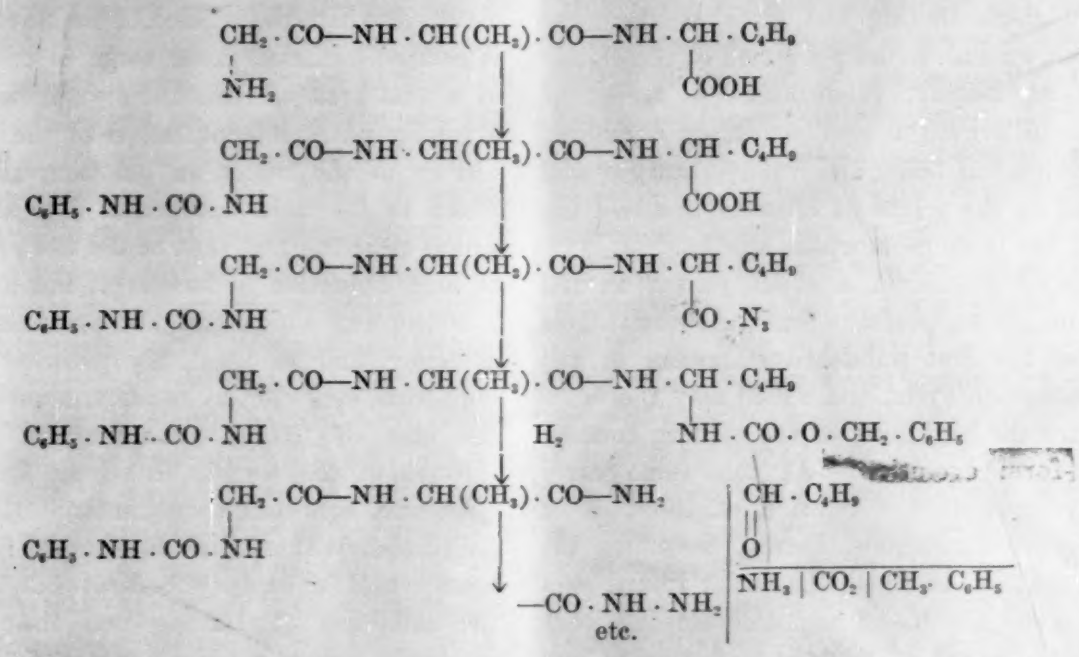
Even after this task has been performed there will remain another fundamental problem, the solution of which is essential to the progress of modern protein chemistry. In order completely to elucidate the structure of the genuine proteins and that of the polypeptides which result from their digestion by proteinases, it is necessary to possess a method for the analytical determination of the mode of arrangement of the constituent amino-acids in the molecules of the proteins and polypeptides, respectively. The importance of this is evident when we consider that the properties of the complete molecule must depend upon the way in which its component parts are arranged. If a protein is subjected to step-wise enzymic degradation the specific mode of action and place of attack of the enzyme can only be explained if the precise arrangement of the component amino-acids in the protein or in its degradation products is known.

The available methods for the analysis of polypeptides and proteins, involving hydrolysis with acids or alkalies, suffer from the disadvantage that all the peptide linkages are simultaneously ruptured, with the resulting formation of difficultly separable mixtures of amino-acids. For our purpose it was necessary to find means of progressively degrading a polypeptide chain such that one amino-acid after an-

other could be detached by procedures which leave the normal peptide linkage intact.

L. Zervas and I have worked out such a method, which I should like to illustrate by the simplest example which we have studied, namely, the tripeptide, glycyl-l-alanyl-l-leucine. The first step is to block the free amino group by substitution. As a substituent we chose in the first place phenyl-isocyanate and prepared a phenylureide of the tripeptide. By thus neutralizing its basic function the tripeptide is converted into a true acid; from this the methyl ester can be prepared under very mild conditions with the aid of diazomethane. The ester is treated with the equivalent amount of hydrazine to yield the hydrazide which in turn is converted according to the method of Curtius into the azide. Such azides on treatment with alcohols readily yield urethanes. The essential point of our method consists in the fact that we choose benzyl alcohol and thus obtain a benzyl-urethane. Now we hydrogenate catalytically this urethane and are able to obtain on the one hand toluene and isovaleric aldehyde and on the other the phenylureide of glycylalaninamide. The original leucine has thus been split off in the form of the easily identifiable aldehyde containing one less carbon atom.

The remaining substituted peptide-amide can now be further treated with an equivalent amount of hydrazine, again converted into a peptide-hydrazide and through the azide with benzyl alcohol into the benzyl-urethane, etc.; the alanine is finally split off as acetaldehyde and can thus be easily identified. In this manner we are able to break down a peptide chain step by step from the carboxyl end obtaining the successive amino-acids in the form of easily recognizable derivatives.[4]



The above work was undertaken in view of the urgent need of improved analytic and synthetic methods for the study of proteins and proteolytic enzymes. Now that some progress has been made in this direction a general plan of attack on the problems of protein constitution lies at hand.

OBITUARY

WILLIAM MORRIS DAVIS

ON the fifth of February last there closed a life which profoundly affected the development of two earth sciences, geology and geography. For more than half a century William Morris Davis was a distinguished leader in these related fields. At the end of this period he possessed, in his eighty-fourth year, the same enthusiasm of purpose, the same flexibility of mind, the same penetrating powers of reasoning which made his career remarkable in the annals of American science. Only a few weeks before his death he crossed the continent during an exceptionally severe winter to deliver the Maiben lecture before the Boston meeting of the American Association for the Advancement of Science. When he lay down to rest his writing table was filled with work actively in progress.

Professor Davis enriched the science of geology by a long succession of able papers based on original studies covering a remarkable range of subjects. In 1882 there began a series of fifteen articles and monographs on the Triassic formations of the Connecticut Valley, out of which came our first full knowledge

[4] This process can no doubt be successfully applied to other classes of compound. Its application to sugars and saccharides is contemplated.

of the intrusive and extrusive trap sheets of this region, our first recognition and location of many oblique faults traversing the formations and our first satisfactory understanding of the extent to which topographic form could be utilized in unraveling faulted structures. To this early period belong papers on details of Appalachian structure in the Hudson Valley, which extended northward the known area of typical Appalachian folding and gave us a clearer conception than we had before possessed of the classic unconformity at Becraft Mountain. A series of papers on the distribution and origin of drumlins, on glacial erosion, on lakes and valleys, gorges and waterfalls and on the origin of cross-valleys laid the foundation of his later geomorphic studies.

In 1884 Davis published a short paper on the classification of plains, plateaus and their derivatives which contains the first published statement of the scheme of the erosion cycle, and which may therefore be held to mark the beginning of the modern conception of land-form evolution. At this same early period, in a report on the relation of the coal of Montana to older formations, Davis recognized the extensive degradation to which the Great Plains province had been subjected, and began developing work on the physical history of rivers which was to culminate in 1889 and 1890 in two brilliant essays: one on "The Rivers and Valleys of Pennsylvania," the other on "The Rivers of Northern New Jersey." These essays, highly original in both content and method, are remarkable for their close analysis of the influence of geologic structures upon stream development at successively lower horizons in strongly folded regions. Although they appeared but a decade after Davis's first published work, they exhibited such a mastery of deductive reasoning and such profound knowledge of the effects of geologic processes upon complex geologic structures that they remain to-day much-quoted classics of American geology.

With the year 1890 began a steady flow of important papers from Davis's skilful pen which at the time of his death, nearly half a century later, continued unabated. It is not possible, within reasonable space, to do more than indicate contributions of exceptional importance. The remarkable versatility of Davis's mind, and the breadth of his interests, is evidenced by papers, monographs and books of a geographical, meteorological and pedagogical character; but we shall for the most part confine our attention to the field in which his chief labors lay, geomorphology. His preparation and training were mainly in the field of geology; he drew his inspiration primarily from the great geologists of the early surveys—Powell, Dutton, Gilbert; and his life work has chiefly been concerned with the study of geological processes, acting on geological structures, through recent geological time.

Davis's "Geological Dates of Origin of Certain Topographic Forms on the Atlantic Slope of the United States" was for a quarter century the fundamental paper on which correlation of geomorphic features in this region rested, and is to-day frequently quoted. His papers on southern New England, in which the scheme of the fluvial erosion cycle is carried to its ultimate stage in the peneplanation of a vast area of resistant crystalline rocks, present a wholly novel interpretation of the later geological history of the region in question, an interpretation which in its main outlines is still accepted. Davis makes clear the fact that he did not originate the idea of land reduction to baselevel; but he gave name to a conception which had not previously gained wide currency, and so effectively pictured the process of land-form evolution by orderly, sequential stages that the idea of fluvial peneplanation spread rapidly throughout the world. In Great Britain the novel American conception encountered the firmly established theory of marine abrasion set forth by Ramsay nearly half a century before; but largely through the influence of Davis's pen the American view gradually gained a place for itself. In France progress was more rapid, while in Germany acceptance of the new idea was aided when Davis by field studies demonstrated peneplanation of the Hunsrück bordering the gorge of the Rhine. Into central Asia Davis carried the new conception of land evolution by demonstrating the peneplaned character of uplifted and tilted blocks of the earth's crust in Tian Shan. Later we find him in South Africa, where he was the first to discover and describe the peneplane of the high veldt and the baselevelling of the Cape Colony ranges. Thus not by his pen alone, but by appropriate field studies in four continents, Davis carried a great American idea to every quarter of the globe. To him, more than to any other, is due the fact that in almost every country where geological studies are prosecuted to-day, the investigator dates a long series of major geological events in terms of ancient erosion planes.

Nor were Davis's foreign studies confined to the problem of peneplanation. In France, Switzerland and Norway he threw needed light on the moot question of glacial erosion. British geologists find in his work on Mount Snowdon the most systematic discussion of alpine glacial erosion in their country; and in his studies of English rivers a new and fertile treatment of stream adjustments in successive erosion cycles. In France we look to Davis for the earliest account of the extensive drainage modifications on structures of the Paris basin. A study of Permian

glaciation in South Africa presents evidence that the ice could not have had its source in a mountainous region, while an account of folded mountains in the same continent traces the evolution of ranges of the Appalachian type. Similarly, in other countries we find his significant contributions to geomorphology in studies of fault phenomena, continental platforms, shoreline evolution and other problems.

No reference to Davis's shoreline studies can be complete which does not record the fact that his contributions in this field opened a new era in shoreline investigations. He closed the door on the old, empirical methods of shoreline description, and pointed the way to a genetic study of the effects of marine processes on variable geologic structures. He showed that there was a cycle of marine erosion just as truly as there were cycles of stream erosion and of glacial erosion. Every modern account of shoreline evolution is a tribute to the genius of William Morris Davis.

In earlier paragraphs emphasis has been placed especially on Davis's original ideas, and only incidentally on work which followed the lead of others. But even where he was not a pioneer Davis made noteworthy contributions to geomorphology. In the Grand Canyon region he was first to discover that the major faulting antedated the "Great Denudation" of Dutton, that the Esplanade had a structural and not a cyclic origin, and that the Colorado was not necessarily an antecedent stream but might more reasonably be interpreted as superposed from a course determined by geologic structures. In a notable series of papers on fault block mountains, he confirmed and extended ideas earlier promulgated by Gilbert, and cast the study of these forms into an entirely new mold by developing to an unprecedented degree the value of physiographic evidence of faulting. His paper on "The Sculpture of Mountains by Glaciers" has been widely quoted because of its artistically eloquent and scientifically convincing comparison of forms found in non-glaciated mountains and in formerly glaciated mountains of similar altitude. To him we owe our first full understanding of the relation of rock defense to the positions and patterns of river terraces, imperfectly appreciated by earlier writers. He added new evidence in support of the fluviatile origin of the fresh-water Tertiaries of the Rocky Mountain region, broadened our understanding of erosion in the Front Range of the Rockies, enriched by field studies our knowledge of desert rock planes in the Southwest, and gave us our first detailed comparison of such planes with those of humid regions. Following the lead of Darwin and Dana in the coral reef problem he visited thirty-five reef-encircled islands of the Pacific, and on the basis of years of study published a long series of articles and a volume indispensable to future workers in this field.

We have touched but a limited portion of Davis's record of scientific productivity. It is a record truly remarkable for breadth of field covered, for penetrating analysis of the problems treated, for quantity of new facts first established, for freshness and vigor of methods employed, and for number of novel and fruitful ideas contributed. His notable achievements in geomorphic research evidence a creative mind of high order whose talents were long and industriously devoted to the service of science. Such achievements could not fail to have a profound influence upon the development of both geology and geography. It is impossible to measure the full extent of that influence; but it is easy to point to evidences of its far-reaching character and to indicate some of the ways in which it has operated.

By his writings Davis practically created a new branch of geology, physiographic geology or geomorphology. Men have, of course, long given attention to the visible manifestations of geologic processes, and great contributions in this field are associated with the names of Hutton and Playfair, Lyell, Geikie and Ramsay, DeLapparent, LaNoë and De-Margerie, Von Richthofen and Penck, Powell, Dutton and Gilbert. But it was Davis who codified the work of these masters into a definite science, unified and vivified by a wholly new conception: the orderly evolution of landforms through systematic stages of development. It was he more than any other who gave precision to this new branch of geology by a large body of critical work, and it was he who had the largest share in creating an "American School" of geomorphology and giving to it international prestige.

By individual studies of high excellence in many foreign lands and by field discussions with foreign investigators on their own territory, Davis initiated a large volume of work in other countries. Thus by personal example and oral teaching he supplemented the labors of his pen in carrying the doctrine of land-form evolution throughout the world. In Europe a great range of geomorphic studies traces its inspiration directly to him. In Asia his studies of the Tian Shan peneplanation were fruitful in later studies widely extending his original ideas. The South African geologists base the later geologic chronology of their region on Davis's study of the high veldt, and describe the evolution of their terrain in terms of his theories of land-form evolution. It is doubtful whether any other American geologist or geographer is so frequently quoted over so great a proportion of the world's surface.

In the development of any science the rôle of the

critic is an important one. There can be no doubt that in this capacity Davis has rendered great service to the related sciences of geography and geology. His many published reviews of geomorphic work at home and abroad not only kept workers in this field in touch with the progress of events, but by their penetrating and constructive criticisms pointed the way to higher achievement. Davis was a crusader in the holy war against archaic theories and careless thinking; and if with the crusader's enthusiasm for a cause he sometimes handled his lance with pitiless skill, the victims have usually lived to forget the pain of criticism in the pride of work yet more skilfully accomplished. Geomorphology has not yet outgrown the faults inherent in the youth of any science; but few will doubt that its achievements are greater in quantity and higher in quality because of the analytical mind and critical powers of William Morris Davis.

Truly great teachers have ever exerted a profound influence upon the growth of a science; and as a teacher Davis was truly great. Through disciples in this and other lands who sat under his instruction in the university, or listened to his teachings in the field, or knew him only through the printed page, Davis has exerted incalculable influence. In the publications of federal and state surveys, in the class work of universities at home and abroad, in the changed scope and emphasis of text books of geology, the effects of his teachings are strikingly apparent. In so minor a matter as the method of illustrating relations of geologic structure to topographic form by block diagrams, one can trace his growing influence in the geologic literature of many countries. And this is but symptomatic of the deeper influence which has transformed the substance of geomorphic literature in every land. Not only in English, but also in German and in French he has carried his teachings to foreign lands both in lectures and in writings. To-day one of the best advanced treatises on geomorphology is his "Erklärende Beschreibung der Landformen," published in Leipzig and Berlin.

It is not easy to determine whether the geologist or the geographer is most greatly in his debt, but there can be no doubt that Davis profoundly affected the development of geography as he did that of geology. For high accomplishment in the geographic field he was admirably prepared first by training in astronomy, and practical work in the National Observatory at Cordoba, Argentina, where he discovered several new variable stars; then by many years of research and teaching in the field of meteorology, bearing fruit in a text book in this subject remarkable for clarity and logical presentation of matter, and a series of original papers which won for him election as corresponding member of the German Meteorological Society; and finally by his still more abundant work on the physiography of the lands. His vision of the field of geography was thus broad as well as penetrating.

It was not surprising that Davis's well-equipped and disciplined mind should bring about a great awakening in American geography. In a long series of papers on the teaching of geography he laid the foundations for a new conception of the subject in which scientifically organized content and scientific methods of instruction should replace a conglomeration of facts empirically presented. In lectures to teachers of geography, in training future teachers in his university classes and seminars, in founding the Association of American Geographers, and in organizing local and international geographical excursions he spread the doctrine of a new geography which should be as truly scientific in content and method as were its sister sciences. Although late in life he wrote that he would not class himself as a geographer, he is known throughout the world as one of the great leaders in this field, one who inspired new life in the geography of his own country and profoundly affected the course of geographic progress in others.

The extraordinary accomplishments of William Morris Davis for the sciences of geology and geography won cordial recognition from his colleagues in both fields. The Geological Society of America bestowed on him its two highest honors: the presidency of the society and the Penrose Gold Medal. The Association of American Geographers placed him twice in the presidency, the American Geographical Society awarded him its Cullum Geographical Medal, the National Council of Geography Teachers its Distinguished Service Award. Twice the British Association for the Advancement of Science made him an honored guest, once in South Africa and once in Australia. Twice he was called as exchange professor to foreign lands, spending one year in Berlin and one year in Paris, in each case lecturing in the language of the nation to which he was accredited. He was the recipient of many medals for signal service in geologic and geographic fields, held honorary doctorates from four foreign universities in three different continents and was elected to honorary membership in the scientific societies of a dozen countries. Few men whose honors came solely as the result of individual scientific labors, and in no degree as executives or other official representatives of great institutions or societies, have been accorded such world-wide distinction.

Among those who knew him intimately the memory of Davis the man will be treasured. His Quaker ancestry was perhaps responsible for a certain rigidity of discipline and a relentlessness in his antagonism to careless thinking which made him a severe master and an uncomfortable opponent. But those who could

endure the discipline and place high value on criticism as helpful as it was keen, found in Davis a loyal friend. He told a man his faults, but told others his virtues. Many a student and younger scientific colleague has learned to his surprise of opportunities opened to him by the quiet but effective intervention of the man who was his most vigorous critic. Beneath a brilliant and incisive intellect beat a warm heart capable of strong affection, whether for a great master like Gilbert or for his own disciples of a younger generation.

DOUGLAS JOHNSON

SCIENTIFIC EVENTS

PEAT INVESTIGATIONS AT THE INTERNATIONAL CONGRESS OF SOIL SCIENCE

THE projected arrangements for the third International Congress of Soil Science, to be held at Oxford, England, from July 30 to August 6, 1935, include a program of the Subcommission for Peat Soils.

As at the previous congress, the interests of American members will find expression in the organization under the chairmanship of Dr. A. G. McCall, the representative of the United States National Section, and Dr. R. V. Allison, chairman of the regional committee.

The outstanding part of the program is to be a major theme dealing with the comparative study of "low moor" peat land from the standpoint of morphological profile features and the influence of drainage on the physical, chemical and biological properties of peat soils. Regional examples will be drawn upon to establish an agreement on methods and technique. The contributions will be summarized in a paper of 30 minutes' duration, to be read at a plenary session of the congress, and to be followed by general discussion.

In addition there will be sessions open to papers and discussions on various subjects in peat investigations, such as surveys performed by government bureaus of different countries, cartographic work and aerial photography, ecological and geographic relationships, changes in climate since postglacial times, localization of peat industries, problems connected with the various uses of peat land resources, highway construction and amelioration.

Another question to be discussed is the classification of peat soils and the terminology required to express new concepts. Lacking any authoritative standard, it is hoped that a tentative statement may be presented to the commission for approval.

It is deemed desirable to stress American attendance and participation in the program. The session is open to any person engaged in some field of peat investigation or interested in its practical application. The British government has taken official cognizance of the International Congress of Soil Science and has invited the United States government to be represented by a limited number of delegates. Attention is directed also to the fact that during the congress facilities will be afforded to visit historic places, and that immediately after the congress there will be a three-weeks tour of England, Wales and Scotland.

Blanks for membership in the congress may be secured from the chairman of the National Section, Dr. A. G. McCall, U. S. Bureau of Chemistry and Soils, Washington, D. C. Manuscripts and reports for the congress are to be sent to Dr. R. V. Allison, at the same address.

THE RAINBOW BRIDGE-MONUMENT VALLEY EXPEDITION

AN expedition to continue exploration of the Rainbow Bridge-Monument Valley area on the Utah-Arizona border, one of the few little-known large areas remaining in the United States, will leave New York on June 28 under the direction of Ansel Franklin Hall, chief forester of the National Park Service.

According to an announcement in *The New York Times*, the tract to be visited, about three thousand square miles in extent, is known from exploration last year to contain interesting archeological, biological and other data. Its scenic features have led to discussion of the area as a national park.

Last year's expedition, under the leadership of Mr. Hall, mapped the principal features of the area, but did not succeed, in the time at its disposal, in reaching the less accessible parts, many of which are believed never to have been seen by a white man. A few Piute Indians, who are being made the basis of an ethnological study, live in the area.

Professor Charles Del Norte Winning, of New York University, has been appointed associate field director. He will be accompanied by about thirty specialists. Fifteen of these have already been appointed. Additional members will include biologists or specialists in particular fields of biology, such as herpetology or ornithology, and architects and artists to survey and sketch Indian cliff and mound dwellings, of which several have been discovered.

Besides Mr. Hall and Professor Winning, the staff as selected to date includes Gerald E. Marsh, of the University of California; John Wetherill, custodian of the Navaho National Monument; John E. Armstrong, of the University of California; Dr. Herbert E. Gregory, of Yale University, director of the Bishop Museum, Honolulu; Professor N. E. A. Hinds, of the University of California; Thorne E. Mayes, engineer of the General Electric Company, and Lyndon L. Hargrave, archeologist.

As was the case last year, the expedition is financed by its members, each being assessed $398. The field

work is expected to require about two months, ending in September.

THE AMERICAN ACADEMY OF ARTS AND SCIENCES

AT the annual meeting of the American Academy of Arts and Sciences, held on May 9, at its house in Boston, the following new members were elected in the scientific classes:

FELLOWS

Class I—Mathematical and Physical Sciences

Franzo Hazlett Crawford, Harvard University
Otto G. C. Dahl, Massachusetts Institute of Technology
Chester Laurens Dawes, Harvard University
Jacob Pieter Den Hartog, Harvard University
Griffith Conrad Evans, Rice Institute, Texas
Jerome Clark Hunsaker, Massachusetts Institute of Technology
Louis Williams McKeehan, Yale University
Donald Howard Menzel, Harvard University
Harry Rowe Mimno, Harvard University
Edward Leyburn Moreland, Boston
Philip McCord Morse, Massachusetts Institute of Technology
Leigh Page, Yale University
Leighton B. Smith, Massachusetts Institute of Technology
John Hasbrouck Van Vleck, University of Wisconsin
David Elbridge Worrall, Tufts College

Class II—Natural and Physiological Sciences

Edgar Anderson, Harvard University
Clarence Gordon Campbell, New York City
Sterling Price Fergusson, Blue Hill Observatory
Cyrus Hartwell Fiske, Harvard University
John Farquhar Fulton, Yale University
Hudson Hoagland, Clark University
Henry Jackson, Jr., Harvard University
Donald Forsha Jones, Connecticut Agricultural Station
Leroy Matthew Simpson Miner, Harvard University
Walter Harry Newhouse, Massachusetts Institute of Technology
William Carter Quinby, Harvard University
Alfred Newton Richards, University of Pennsylvania
Oscar Riddle, Cold Spring Harbor, N. Y.
Carl-Gustaf Arvid Rossby, Massachusetts Institute of Technology
Arthur Hiler Ruggles, Providence, R. I.
Edmund Ware Sinnott, Columbia University
Gilbert Morgan Smith, Stanford University

FOREIGN HONORARY MEMBERS

Ronald Aylmer Fisher, London
Archibald Vivian Hill, London
Arthur Holmes, Durham, England
Paul Janet, Paris
Luigi Lombardi, Rome
Richard Willstätter, Munich

The following officers were elected for the year 1934–1935:

President, George Howard Parker
Vice-President for Class I, James Flack Norris
Vice-President for Class II, Walter Bradford Cannon
Vice-President for Class III, Edwin Francis Gay
Vice-President for Class IV, Arthur Stanley Pease
Corresponding Secretary, Tenney Lombard Davis
Recording Secretary, Walter Eugene Clark
Treasurer, Ingersoll Bowditch
Librarian, Alfred Church Lane
Editor, Robert Payne Bigelow

THE MEDAL MEETING OF THE FRANKLIN INSTITUTE

THE medal meeting of the Franklin Institute was held on the afternoon of May 16 and in the evening a dinner was given in honor of the medalists.

Franklin Medals with certificates of honorary membership were presented to Dr. Henry Norris Russell, research professor of astronomy at Princeton University and director of the observatory, for his "pioneer work in the application of physical theories to astronomical problems," and to Dr. Irving Langmuir, associate director of the Research Laboratories of the General Electric Company at Schenectady, "in recognition of his investigations in physics and chemistry." Dr. Russell spoke on "The Atmospheres of the Stars" and Dr. Langmuir on "The Mechanical Properties of Monomolecular Oil Films."

The other awards were:

The Longstreth Medal, William Edwin Sykes, Buffalo, New York.
The Wetherill Medals, Dr. Johann B. Ostermeier, Augsburg, Germany; Dr. E. Newton Harvey, Princeton University, and Alfred Lee Loomis, Tuxedo Park, New York.
The Levy Medal, Dr. Kenneth T. Bainbridge, Cambridge, England.
The Potts Medal, Ernst Georg Fischer, Washington, D. C.
The Cresson Medals, Stuart Ballantine, Boonton, New Jersey; Union Switch and Signal Company, Swissvale, Pennsylvania.
Certificates of Merit, Albert Allen, Winchester, Massachusetts; Joseph Grundy Shryock, Philadelphia.

SCIENTIFIC NOTES AND NEWS

DR. GEORGE CARY COMSTOCK, director emeritus of the Washburn Observatory and professor of astronomy in the University of Wisconsin, formerly dean of the Graduate School, died on May 11 in his eightieth year.

DR. HARLOW SHAPLEY, of the Harvard College Observatory, delivered the George Darwin Lecture before the Royal Astronomical Society on May 11. At the conclusion of the lecture, Professor F. J. M. Stratton, professor of astrophysics at the University

of Cambridge, presented to Dr. Shapley the gold medal of the society for his work on "one of the major problems of the universe," and also for his earlier researches on variable stars. Dr. Edwin P. Hubble, of Mount Wilson Observatory, then reciprocated the honor paid to Dr. Shapley by presenting the Bruce Medal of the Astronomical Society of the Pacific to Dr. Alfred Fowler, professor of astrophysics at the University of London and Yarrow research professor at the Royal Institution. Dr. Hubble expressed the appreciation of American astronomers for Dr. Fowler's work on solar and stellar spectra.

THE medal of the American Institute of Chemists, presented annually "for noteworthy and outstanding service to the science of chemistry and the profession of chemistry in America," has been awarded this year to Dr. James Bryant Conant, president of Harvard University. The award is made in recognition of Dr. Conant's many contributions to the science of chemistry and for his eminence as a professional chemist. The medal will be presented to Dr. Conant at the annual meeting of the American Institute of Chemists, on May 21. Dr. Hans T. Clarke, professor of biological chemistry at Columbia University, has been selected to make the presentation. Dr. John H. Finley, of *The New York Times,* will be among the speakers of the evening.

THE Herty Medal, given annually by the Chemistry Club of the Georgia State College for Women at Milledgeville for "the most outstanding research in chemistry in the southeastern states" was awarded this year to Dr. Charles H. Herty, for his work on the use of Georgia slash pine in the manufacture of paper. The presentation took place on May 5, at a meeting of the Georgia Section of the American Chemical Society. Dr. J. Sam Guy, of Emory University, made the presentation to Dr. Herty, who responded. In his address in the evening Dr. Herty gave an account of the work on which the award was based.

AT the recent meeting of the American Mathematical Society in Chicago, the dinner program was in honor of Emeritus Professor Thomas F. Holgate, of Northwestern University, and Emeritus Professor Herbert E. Slaught, of the University of Chicago. Each had been secretary of the Chicago Section of the society for a ten-year period and each had served his university continuously for more than forty years. Professor Slaught had been made honorary president for life of the Mathematical Association of America, at its previous Cambridge meeting. Addresses were made by Professors F. R. Moulton, L. E. Dickson, D. R. Curtiss, G. A. Bliss and W. C. Graustein, and Professor Holgate and Professor Slaught responded.

JOSIAH K. LILLY, of Indianapolis, was elected honorary president of the American Pharmaceutical Association following the dedication of the new building of the association on May 9.

SIR RICHARD STAWELL, honorary consulting physician to the Melbourne Hospital and Children's Hospital, Melbourne, has been nominated as president of the British Medical Association for 1935–36. The annual meeting of the association will be held at Melbourne next year, and in 1936 at Oxford. An invitation has been received to hold a future annual meeting, preferably after 1940, in South Africa. Lord Dawson of Penn and Sir Henry Brackenbury, chairman of the council, have been elected vice-presidents of the association.

PROFESSOR GEORGE GAMOW, of the Leningrad Polytechnical Institute, will be the foreign visiting member at the twelfth annual physics symposium during the summer session of the University of Michigan. Professor J. Robert Oppenheimer, of the California Institute of Technology, will be the American visiting member.

DR. ALEXANDER H. PHILLIPS, chairman of the department of geology at Princeton University, will retire from active service in June, but will continue as lecturer in geology.

DR. E. H. BARBOUR will retire in June as head of the department of geology at the University of Nebraska, after serving for forty-three years. He will retain the directorship of the University Museum and will also hold the title of professor of paleontology. Dr. Barbour will be succeeded by Professor E. F. Schramm. Professor Schramm has been a member of the department of geology since 1908 and professor of geology since 1918. Dr. A. L. Lugn, who became a member of the faculty in 1927, was recently promoted from an assistant professorship to an associate professorship of geology.

AT the annual meeting of the American Association of Physical Anthropologists, held in conjunction with the American Society of Mammalogists, from May 8 to 10, at the American Museum of Natural History, the following were elected officers of the society: Professor Raymond Pearl, *president;* Dr. H. L. Shapiro, *secretary-treasurer;* Professor T. Wingate Todd, *member of the executive committee.*

OFFICERS of the Association of American Physicians were elected at the Atlantic City meeting as follows: Dr. Henry A. Christian, Hersey professor of the

theory and practise of physic at Harvard University, *president;* Dr. Rollin T. Woodyatt, professor of medicine at the Rush Medical College of the University of Chicago, *vice-president,* and Dr. James H. Means, Jackson professor of clinical medicine at the Harvard Medical School, *secretary.* Dr. Louis Hamman, associate professor of medicine at the Johns Hopkins University, was chosen *councilor.*

DR. WILLIAM FOGG OSGOOD, Perkins professor of mathematics, *emeritus,* at Harvard University, has accepted an invitation to join the department of mathematics at the National University of Peking. He expects to sail early in August.

DR. ALFRED C. REDFIELD, professor of physiology, has been appointed director of the Biological Laboratories of Harvard University, a post created to make more effective the consolidation of the departments of botany, zoology and general physiology into a department of biology.

As the first incumbents of a series of exchange professorships between the Massachusetts Institute of Technology and other educational institutions, Professor Harold L. Hazen, of the department of electrical engineering, has been appointed to serve next year as a member of the faculty of the Ohio State University, and Professor J. F. Byrne, of the electrical engineering department of the Ohio State University, will spend the coming year at the institute.

PAUL W. CHAPMAN has been appointed dean of the Georgia College of Agriculture, relieving H. P. Stuckey, who continues as director of the station.

H. P. BARSS, professor of botany and plant pathology and plant pathologist in the Oregon College and Station, has been appointed principal botanist.

DR. FRANK H. LATHROP has been appointed entomologist at the Maine Agricultural Experiment Station to succeed the late Dr. Clarence R. Phipps.

DR. WILLIAM H. F. WARTHEN, for ten years director of the Bureau of Child Welfare, has been appointed assistant commissioner of health of the Baltimore City Health Department, succeeding the late Dr. John Frederick Hempel.

DR. JACOB G. LIPMAN, dean of the College of Agriculture and director of the New Jersey State Agricultural Experiment Station, has been given a year's leave of absence from Rutgers University, beginning on July 1. Dr. Lipman will direct an inventory of the soil fertility resources of the United States to be made by the U. S. Department of Agriculture. The inventory will aim to provide a more accurate basis for the determining of national policies "on the use of land for agriculture, forests, recreation and other purposes, and to point the way to a more effective conservation of the plant food resources of soils."

DR. HOWARD E. SIMPSON, professor and head of the department of geology and geography of the University of North Dakota and state geologist, has been appointed by Secretary Ickes to conduct a study of ground water fluctuations in North Dakota, the eastern portions of South Dakota, Nebraska and Kansas, and the western portions of Minnesota, Iowa and Missouri. The work will be done under the supervision of the Mississippi Valley Committee of the Federal Emergency Administration of Public Works. The study forms a part of the general investigation of rainfall, run-off and ground water conditions now being conducted by the U. S. Geological Survey and other agencies under a recent Public Works Administration allotment, looking toward a relief of the water problem in the northwestern states.

DR. GEORGE A. HULETT, professor of physical chemistry at Princeton University, has leave of absence next year for the second term.

DR. HARRY STEENBOCK, professor of agricultural chemistry at the University of Wisconsin, and Dr. E. M. Nelson, of the Vitamin Testing Laboratory of the Bureau of Chemistry and Soils of the U. S. Department of Agriculture, have been invited to represent the United States before the Permanent Commission on Biological Standardization of the League of Nations at a conference to be held in London, from June 12 to 14.

DR. ANTON J. CARLSON, Frank P. Hixon professor of physiology and chairman of the department of physiology at the University of Chicago, delivered the annual Frederick A. Packard memorial lecture of the Philadelphia Pediatric Society on April 10, on "The Mechanism of Appetite, Hunger and Thirst."

DR. OSKAR BAUDISCH, of Yale University, formerly of the University of Zürich and the Rockefeller Institute, addressed the Priestley Club of the department of chemistry and chemical engineering of the University of Pennsylvania on May 3. His subject was "Active Iron—its Chemical and Biological Aspects."

DR. A. O. LEUSCHNER, professor of astronomy at the University of California, was recently a guest of the Sigma Xi Club of the University of Denver. He spoke on "Effective Research" at a luncheon given in his honor.

DR. C. H. ANDREWS delivered the Oliver-Sharpey lectures of the Royal College of Physicians on May 1 and 3 on "Viruses in Relation to the Etiology of Tumors" and Professor O. L. V. S. de Wesselow will

deliver the Croonian Lectures on June 5, 7 and 12, on "Arterial Hypertension."

THE sixteenth annual meeting of the New Hampshire Academy of Science will be held on Friday and Saturday, June 1 and 2, at the Hancock Hotel, Hancock, New Hampshire, under the presidency of Samuel P. Hunt, of Manchester.

THE American Dairy Science Association will hold its annual meeting at Cornell University and the New York State Agricultural Experiment Station at Geneva from June 26 to 28. The first two days will be spent at Ithaca and the third day at Geneva. Formal programs will be presented at both places.

BY the will of the late William H. Welch, his medical, scientific and literary books with medals go to the Johns Hopkins University. These include a rare collection of medical portraits and pamphlets, to be dedicated preferably to the Institute of the History of Medicine and the School of Hygiene and Public Health. The university is to make a selection from these gifts. Should there be any the university does not desire, the rejected part of the collection will go to Alexander G. Wolcott, a grandnephew. The residue of the estate is divided into four parts, one part to be given to the Johns Hopkins Endowment.

THE $25,000 gift to the Long Island College of Medicine from the Misses Jennie A. and Cornelia Donnellon has been utilized, according to their wishes, in the purchase of their former residence adjoining the college and in equipping it as a student recreation center. The basement has been converted into a cafeteria; the first floor consists of lounge rooms and card room; the second and third floor of study and game rooms.

A TRUST fund of approximately $200,000 has been created by anonymous donors to be used over a period of ten years for the establishment and maintenance of a department for research into the causes and cure of cancer in the Hebrew University at Jerusalem. Part of the available funds will be used for the erection and adequate equipment of special laboratories.

J. D. WATSON has given to the University of Georgia a tract of 609 acres, including Watson Springs, to establish a research station in animal husbandry and forestry.

A COLLECTION of 835 ethnological specimens from the Pacific islands of the Melanesian and Polynesian groups has been presented to the Field Museum, Chicago, by Templeton Crocker of San Francisco.

THE order issued soon after the establishment of the Department of Commerce and Labor, changing the name of the National Bureau of Standards to the Bureau of Standards, has been rescinded. Measuring apparatus certified by the bureau was from that time stamped "BS" instead of "NBS." But "BS" was also stamped on measuring instruments by State Bureaus of Standards, by one manufacturer and by the British Standards Institution. From now on the stamp of the bureau will bear the former letters, "NBS." This symbol is unique and free from ambiguity.

UNDER allotments from the Public Works Administration, the United States Geological Survey is undertaking four projects in Texas. These are quicksilver and silver of the Terlingua and Shafter districts; bleaching clay and other high-grade clay of the San Antonio area; the brown iron ore of northeast Texas, and the oil, gas and coal of north-central Texas. The study of the quicksilver and silver has been initiated with C. P. Ross, of the United States Geological Survey, in charge. The clay project, under the direction of Philip King, will be initiated this month, as will the survey of the iron ore deposits, conducted by G. C. Eckel. The oil, gas and coal study of north-central Texas will be directed by N. W. Bass, of the United States Geological Survey. The four projects are to be completed not later than June, 1935.

ACCORDING to *Nature*, at the twelfth annual corporate meeting of the Institution of Chemical Engineers presentation was made of the Moulton Medal, the Junior Moulton Medal and Prize of books, and the Osborne Reynolds Medal, all of which were instituted in 1929. The Moulton Medal, which commemorates the chemical engineering work of the late Lord Moulton at the Department of Explosives Supply, is awarded for the best paper of each year presented before the institution. Papers by non-members of the institution are eligible for this medal. For 1933 the award is made for the following papers: "The Mechanical Properties of Some Austenitic Stainless Steels at Low Temperatures," by E. W. Colbeck, W. E. MacGillivray and W. R. D. Manning, and "The Mechanical Properties of Metals at Low Temperatures. (2)—Non-Ferrous Materials," by E. W. Colbeck and W. E. MacGillivray. The Junior Moulton Medal is given for the best paper of the year read before the graduates and students section of the institution. Only papers by graduates and students of the institution are considered for this medal and prize. For 1933 the award is made for the paper: "The Solvent Extraction of Sulphur from Sicilian Ores," by Dr. E. H. T. Hoblyn. The Osborne Reynolds Medal commemorates the fundamental investigations of the late Professor Osborne Reynolds, and is awarded for meritorious service for the advancement of the institution. For 1933 the award is made to H. W. Cremer. Mr. Cremer acted as honorary secretary of the institution during the illness of

the late Professor J. W. Hinchley in 1931, and was appointed to succeed Professor Hinchley in that office on the latter's death.

THE report of the council of the Zoological Society of London shows that the number of visitors to the gardens during December was 19,887, the receipts amounting to £387. The total number of visitors for the year up to the end of December was 1,557,791, and the receipts £47,536, showing a decrease of £353 as compared with the same period of the previous year and a decrease of £14,635 as compared with the average for the corresponding period of the previous five years. The number of visitors to the aquarium during December was 4,792, the receipts amounting to £116. The total number of visitors for the year was 263,438, the receipts amounting to £8,820, showing a decrease of £331 as compared with the same period of the previous year. The number of visitors to Whipsnade Park during December was 1,278, the receipts for admission amounting to £70. For the year the visitors numbered 433,429, the receipts amounting to £18,759, showing a decrease of £3,364 as compared with the corresponding period of the previous year. There were 444 fellows elected and readmitted during the year, an increase of 63 on the year before and a decrease of 120 compared with the average for the corresponding period of the previous five years.

THE British Ministry of Agriculture states that an order has been made by the minister under the Destructive Insects and Pests Acts, 1877 to 1927, and by arrangement with the Forestry Commissioners under the Forestry Act, 1919, with the object of preventing the introduction into Great Britain of diseases which might prove injurious to forest trees. This order, which is entitled the Importation of Elm Trees and Conifers (Prohibition) Order of 1933, and came into operation on December 1, 1933, prohibits the landing in England or Wales from any country other than Scotland, Northern Ireland, the Irish Free State, the Isle of Man, or the Channel Islands of any living plants of the following eight genera of the Order *Pinaceae: Abies, Larix, Picea, Pinus, Pseudotsuga, Sequoia, Thuja* and *Tsuga*. The importation of living trees from any European country has been prohibited since January 15, 1927, by the Importation of Elm Trees (Prohibition) Order of 1926. That order is now revoked, but its provisions have been embodied in the new order and extended to elm trees from any country other than those mentioned in the preceding paragraph. The order further requires that the health certificates prescribed under the Importation of Plants Order of 1933 to accompany living plants imported from abroad must include a statement to the effect that the consignment does not contain any plants of the genera now prohibited.

DISCUSSION

IONIZED ARGON IN THE SPECTRUM OF UPSILON SAGITTARII

WHILE attempting to identify the many peculiar lines in the spectrum of the supergiant Upsilon Sagittarii I have found that all of the strong lines in the laboratory spectrum of *A* II coincide with faint lines in the spectrum of the star. Of sixteen argon lines which are present nine are sensibly unblended. The two strongest laboratory lines in the spectral range λλ 4000–4900, located at λλ 4348 and 4806, are represented by unblended lines of moderate intensity in the stellar spectrum. Several of the lines are included in J. S. Plaskett's[1] list of wave lengths; the others were measured on Yerkes one prism spectrograms.

W. W. MORGAN

YERKES OBSERVATORY,
WILLIAMS BAY, WISCONSIN,
MAY 8, 1934

THE ROTATION OF THE EARTH

A CORRESPONDENT of the Smithsonian Institution, Mr. W. F. Fletcher, writes: ["Owing to] the heating and consequent expansion of the atmosphere, offering a greater depth of atmosphere on the afternoon side of the earth than on the forenoon side, the increase of leverage [for the action of light pressure] on the eastern limb would tend to cause or maintain a west to east movement [as seen] in the known rotation of the earth."

I do not recollect to have seen this suggestion in the literature. Can any of your readers inform me if it is old? Apparently the sun must thus exercise an accelerating influence. It would be interesting for some one to compute how large this is compared to the sun's retarding influence through the tides.

C. G. ABBOT

SMITHSONIAN INSTITUTION

THE ISOTOPIC FRACTIONATION OF WATER BY PHYSIOLOGICAL PROCESSES—AN ADDITION

DURING the course of an investigation, still in progress, on the separation of the isotopes of hydrogen and oxygen by the electrolysis of water, it has been found that commercial oxygen prepared by the fractionation of liquefied air is slightly heavier than

[1] Publications of the Dominion Astrophysical Observatory 4: 115, 1928.

atmospheric oxygen.[1] The increase amounted to 2.2 ppm for the oxygen tested from a certain commercial cylinder. At the same time that the measurements which demonstrated this difference were being made, Klar and Krauss[2] announced the discovery that the oxygen escaping with the nitrogen at the top of a column for fractionating liquid air is lighter than atmospheric oxygen and that the last portion of oxygen left after the fractionation of a charge of liquid air is heavier than normal. Their discovery has accordingly been confirmed, and in addition the magnitude of the difference to be expected in commercial oxygen from liquefied air has been established.

In a recent article in this journal,[3] it was reported that the water obtained from the sap of a young willow tree was heavier than normal by 2.9 ppm, and the water obtained by burning the dry wood in a current of dry oxygen was heavier than normal by 5.4 ppm. No explanation of the difference of 2.6 ppm between these values was offered at the time, but it is now clear that this increase was contributed by the commercial oxygen used in the combustion. It was also reported that the density difference of 5.4 was reduced to 3.1 ppm by repeated saturation and desaturation with dry gaseous ammonia. It is now clear that no further reduction in density difference was possible by this method because the remaining difference was contributed by the commercial oxygen. This additional information, however, does not change but rather serves to clarify the results and conclusions of the previous article.

EDGAR R. SMITH

BUREAU OF STANDARDS,
WASHINGTON, D. C.

ISOTOPIC CO_2 AND O_2 IN PLANTS?

WASHBURN and Smith report that the sap and combined H_2 in the wooden part of a growing willow tree yield heavy water. There appears to be a preferential selection of heavy H_2 isotopes in the process of synthesis of organic compounds.

Barnes observed the inactivation "in vivo" of certain enzymes in dilute heavy water. Barnes, Richards and Meyer conclude that high concentration heavy water has a lethal effect on plants while dilute heavy water shows a stimulating action.

It appears from such work that the water absorbed by plants for their physiological processes probably differs isotopically from the water lost during such processes.

This would suggest that CO_2 absorbed during the photosynthetic process and the O_2 absorbed during the respiratory process differ isotopically from the O_2 rejected during the photosynthetic process and the CO_2 rejected during the respiratory process.

ANDREW MOLDAVAN

MONTREAL, CANADA

THE CONTROVERSY CONCERNING THE PHYSIOLOGICAL EFFECT OF TRIHYDROL IN LIQUID WATER

A NOTE by Ellis and Sorge[1] reported that recently condensed water and water from freshly prepared ice showed similar infra-red absorption curves. The experiments were intended to throw light on the biological effects of ice water and steam water, but no mention is made of similar tests both positive and negative. There is no doubt concerning the physiological importance of trihydrol as an equilibrium constituent of water. As Duclaux[2] points out (from analogy with H_2S, etc.), water should boil about 100° below zero if it were not composed of aggregates. Properties which render water suitable as a life medium are due to its content of liquid ice, *i.e.*, the high specific heat is the heat of dissociation of trihydrol.

The estimates of the equilibrium concentration of hydrols are remarkably similar (*cf.* Whiting,[3] Sutherland,[4] Richards and Chadwell,[5] Rao[6]). Ice water has a favorable effect on the longevity of *Spirogyra* and stimulates cell division in *Euglena*,[7] and Harvey[8] has recently shown that the addition of ice water to sea water stimulates the growth of *Nitzschia*. It is possible that the equilibrium concentration of hydrols in ice water is not instantaneous, for experiments of Howard T. Barnes[9] indicate a lag in the polymer equilibrium during the exhaustion of the ice-forming power of water. In a typical experiment in a large water tank (−10° C.) the first hour yielded 8 pounds of ice, the second hour six pounds, the third hour five pounds, the fourth hour four and one half pounds, etc., until the ice-forming power of the water was practically exhausted. Other experiments[10] have shown that water from ice consisting of large crystals, warmed to 10° C. and placed in Dewar flasks at −5° C., will freeze more rapidly than recently condensed water under the same conditions. According to the colloidal theory, ice water freezes more rapidly

[1] E. R. Smith, *J. Chem. Physics*, 2: 298, 1934.
[2] R. Klar and A. Krauss, *Naturwissenschaften*, 22: 119, 1934.
[3] E. W. Washburn and E. R. Smith, SCIENCE, 79: 188, 1934.

[1] Ellis and Sorge, SCIENCE, 79: 370, 1934.
[2] Duclaux, *Rev. gen. Sci.*, 23: 881, 1912.
[3] Whiting, "A New Theory of Cohesion Applied to the Thermodynamics of Liquids and Solids," Cambridge, Mass., 1884.
[4] Sutherland, *Phil. Mag.*, 50: 460.
[5] Richards and Chadwell, *Jour. Am. Chem. Soc.*, 47: 2283, 1925.
[6] Rao, *Nature*, 132: 480, 1933.
[7] Barnes and Jahn, *Proc. Nat. Acad. Sci.*, 19: 638, 1933.
[8] Harvey, *Jour. Mar. Biol. Assoc.*, 19: 253, 1933.
[9] H. T. Barnes, *Sci. Monthly*, 29: 289, 1929.
[10] Barnes and Jahn, *ibid.*

because it takes less time to reach the saturation point of trihydrol. Bancroft and Gould[11] object that water has not a variable freezing point like acetaldoxime, but we refer to the *time* required for freezing.

Wills and Boeker[12] describe a hysteresis in the diamagnetic susceptibility of water, depending on its thermal history. This is not due to the apparatus[13] used, since other substances (carbon tetrachloride, toluene) do not show the lag. Some diamagnetic methods,[14] however, do not demonstrate the polymer hysteresis. Some years ago Baker[15] suggested that association takes place more slowly for liquids than for gases, *i.e.*, water heated at 80° C. for 48 hours (in presence of a catalyst) may exhibit an altered vapor pressure which persists for days.

Ellis and Sorge do not mention negative evidence supporting their own results. Menzies[16] tested my trihydrol hypothesis by comparing the vapor pressure of boiled (not steam) water and water from freshly prepared ice (fine needle crystals) by means of a water manometer. No appreciable vapor pressure difference was detected by this method, but Menzies used a small sample of freshly frozen water and boiled water, whereas the best biological results are found in water from aged block ice (large crystals) as compared to freshly *condensed* water. La Mer and Miller[17] suggest that Menzies' method was not sufficiently sensitive to detect small differences in polymers, although they find no difference in the refractive index of distilled water of different ages. Menzies expected a greater vapor pressure difference near 0° C. than at 25° C. in spite of the fact that 0° C. is the triple point at which the vapor pressure of ice (almost 100 per cent. trihydrol) and water (37 per cent. trihydrol) are the same (*i.e.*, both 4.579). Ice itself evaporates as a solid vapor.[18] Menzies[19] previously claimed that water vapor contains no polymers, but this was corrected by Maass and Mennie.[20] Vapor pressure may indicate activity of water molecules at the surface, but it fails to indicate bound[21] water demonstrated by other methods.[22]

Like Menzies, Ellis and Sorge use water from a small sample of freshly prepared ice, but x-ray studies[23] have shown that such samples do not yield single crystals with well-developed faces for which commercial block ice must be used. Plyler[24] states that the best crystals for infra-red studies are obtained by aging commercial block ice for two months (slightly below 0° C.) in which 5-inch crystals develop. The growth of ice crystals with age has not been explained, but Altberg and Troschin[25] have published beautiful photographs of single ice crystals half a meter in size found in caverns in the Ural Mountains. According to Plyler, the infra-red absorption of water and ice are similar, for both have a dielectric constant of about 80 for long waves. Ice has the corresponding infra-red bands of liquid water, but they are shifted slightly toward the longer wavelengths. Now, according to Sutherland, water at 0° contains 37 per cent. trihydrol and ice is almost 100 per cent. trihydrol, yet the differences in most of the infra-red bands are only a few units in the second decimal place, so that a 10 per cent. polymer difference in ice water would not be clearly indicated in Sorge and Ellis' method. Moreover, in one case Plyler found the bands of water and ice the same, due to a water film in the latter. Also, the temperature shift[26] in the infra-red bands of liquid water is much smaller than the polymer change. Ellis and Sorge used ice water at 21° C., while in our biological experiments the ice water is added at 10° C. Temporary exposure to cold water (high polymerization) may enable the cells to bind trihydrol, since Kolkmeijer and Favejee[27] find that the bound water in emulsoid sols is arranged in the ice lattice.

Bancroft and Gould suggest that our results may be due to an unsuspected impurity or to the presence of the hydrogen isotope. The impurity explanation is improbable, since clear block ice yields dust-free conductivity water and there is no significant pH difference indicating a different CO_2 content in the water samples (which were bubbled with O_2 in some cases). Also Harvey obtained the biological effect, under certain conditions, in sea water, which eliminates a salt effect.

It is probable, however, that the heavy isotope of hydrogen influences the polymerization, since Bingham and Stevens[28] find that concentrated heavy water is inert due to low association (low trihydrol content) and, as Frerichs[29] remarks, workers on the biological effect of concentrated heavy water have not

11 Bancroft and Gould, *Jour. Phys. Chem.* 38: 197, 1934.
12 Wills and Boeker, *Phys. Rev.*, 42: 687, 1932.
13 Boeker, *Phys. Rev.*, 43: 756, 1933.
14 Cabrera and Fahlenbach, *Zeit. Phys.*, 82: 759, 1933.
15 Baker, *Jour. Chem. Soc.*, 130: 949, 1927.
16 Menzies, *Proc. Nat. Acad. Sci.*, 18: 567, 1932.
17 La Mer and Miller, *Phys. Rev.*, 43: 207, 1933.
18 H. T. Barnes, "Ice Engineering," Renouf, Montreal, 1928.
19 Menzies, *Jour. Am. Chem. Soc.*, 43: 851, 1921 .
20 Maass and Mennie, *Proc. Roy. Soc.*, 110A: 198, 1926.
21 Hill, *Proc. Roy. Soc.*, 106B: 477, 1930.
22 Gortner and Gortner, *Jour. Gen. Physiol.*, 17: 327, 1934.
23 W. H. Barnes, *Proc. Roy. Soc.*, 125A: 670, 1929.
24 Plyler, *Jour. Optical Soc. Amer.*, 9: 545, 1924.
25 Altberg and Troschin, *Naturwissenschaften*, 19: 162, 1931.
26 Collins, *Phys. Rev.*, 26: 771, 1925.
27 Kolkmeijer and Favejee, *Nature*, 132: 602, 1933.
28 Bingham and Stevens, *Jour. Chem. Phys.*, 2: 107, 1934.
29 Frerichs, *Naturwissenschaften*, 22: 113, 1934.

considered the polymerization factor. Uhlmann[30] has suggested that an isotopic fractionation occurs in the sublimation of ice and snow, which would mean that our aged ice samples contained more deuterium than the condensed water; and the first biological experiments[31] with heavy water showed that a concentration slightly higher than that in "ordinary" water (if there is such a substance) has a beneficial effect on *Spirogyra*.

The term "trihydrol" has been used for the highest polymer, but this may be an aggregate of as many as twenty-three molecules,[32] hexahydrol,[33] a quartz-like structure,[34] or a doublet of the pyramidal anion H_3O_2 with the hydrogen ion.[35] Since the polymers differ in density (Sutherland calculates the density of trihydrol as 0.88) separation might be effected by other methods. Berkeley[36] has suggested centrifugal force for the separation of isotopes and polymers, and perhaps ultracentrifuges like those of Svedberg[37] or Beams and Pickels[38] will ultimately develop fields of sufficient magnitude.

The conclusion appears to be that, although ice water and steam water have different biological effects, a good deal more information is needed on the physical side before definite rôles can be assigned to the many forms of water in living matter.

T. CUNLIFFE BARNES
OSBORN ZOOLOGICAL LABORATORY
YALE UNIVERSITY

A POSSIBLE EXPLANATION OF THE FUNCTION OF GLUTATHIONE IN DEVELOPMENTAL GROWTH

FOR the past two and a half years I have been studying the developmental reaction of *Obelia geniculata* to the naturally occurring tissue "Bausteine." Since some time must elapse before the data as a whole will be published, I am reporting the essence of the results with the three amino-acids of which glutathione is composed. These results derive from observation of the development of some thousands of animals under conditions described in previous papers. As has been told in many reports, the chief function of cystine or cysteine, its reduced form, in developmental growth is acceleration of cell multiplication. This derives from the SH group potentially or actually contained therein. Glycine, a second of the amino-acids of glutathione, has now been found to favor the regeneration of new hydranths from broken pedicels. No other amino-acid does this specifically. The finding suggests that glycine is concerned in the protein reconstitution essential for regeneration. It is perhaps a scientific demonstration of why gelatin with its high glycine content has been popularly supposed to be particularly useful as an article of diet in convalescence from wasting disease. It is consistent with the recent reports in medical literature that in some cases glycine is apparently of benefit in rebuilding muscle tissue. The third amino-acid of glutathione is glutamic acid. And this decidedly and definitely favors the process of differentiation and consequent organization. No other amino-acid yields like effect to like degree. It is this amino-acid which shows as its outstanding and specific influence upon developmental growth the acceleration of differentiation and consequent organization.

Thus, then, it seems as if in glutathione nature has developed in one and the same chemical compound a complex which conditions if it does not determine the course of the several basic and essential processes concerned in developmental growth. Through cysteine it accelerates cell proliferation, the first step; through glycine it accelerates that protein reconstitution which is an essential accompaniment to both cell division and cellular differentiation; and through glutamic acid it accelerates the progress of that selective building-up of the protein molecule which is the characterizing process of differentiation and its consequent organization.

There are those who deprecatingly insinuate that reports of what happens under certain conditions are of little value without explanations of the mechanism producing the given reaction. It takes but little clear thinking to realize that the first step in scientific inquiry is to find out what happens. Only when this has been done can there be found out how it happens. The why is so frequently a subject of metaphysics that it need not be discussed here.

FREDERICK S. HAMMETT
MARINE EXPERIMENTAL STATION
NORTH TRURO, MASS.

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A METHOD FOR DESTROYING INTERNAL CELL MASSES

THE problem of destroying internal cell masses with a minimal destruction of the intervening layers of tissues has arisen in a number of different fields of research. Most of the techniques thus far devised have certain limitations which obviate their use in investigations where a precise control over the amount

[30] Uhlmann, *Naturwissenschaften*, 22: 119, 1934.
[31] Barnes, *Jour. Am. Chem. Soc.*, 55: 4332, 1933.
[32] Duclaux, *Compt. rend. Acad. Sci.* 152: 1387, 1911.
[33] Pennycuick, *Jour. Phys. Chem.*, 32: 1681, 1928.
[34] Bernal and Fowler, *Jour. Chem. Phys.*, 1: 515, 1933.
[35] Kinsey and Sponsler, *Proc. Phys. Soc.*, 45: 768, 1933.
[36] Berkeley, *Nature*, 120: 840, 1927.
[37] Svedberg, SCIENCE, 79: 327, 1934.
[38] Beams and Pickels, *Jour. Chem. Phys.*, 2: 143, 1934.

and locus of the destroyed region is an important desideratum. The older methods of destruction by mechanical means, such as by the use of a scalpel, brain knife or especially devised trephine, do not allow for this precise control. They can not be used for destroying internal cell masses when the destruction of the overlying tissues is to be held at a minimum. Adequate control is also lacking in the method involving the injection of chemicals into the parts to be affected. Although the intervening tissue destroyed may be reduced to an exceedingly small amount, it is impossible to accurately control the locus and size of the regions infiltrated with the chemical.

The electro-cautery method offers a more accurate control over the amount of destruction and has proved extremely valuable for ablating external layers of tissue. It is not used for destroying internal masses. High frequency currents have likewise offered a means for attaining an accurate control over the amount and locus of the region affected. They have been used with marked success by surgeons in the removal of various types of neoplasms, and a rather refined technique of electro-surgery has resulted from this particular application. These currents have also been used for heating internal cells masses, even to lethal temperatures. No account has been found of high-frequency currents being conducted into the inner parts of a tissue by means of an insulated electrode, thus producing localized destruction of cells.

In endeavoring to study the functions of certain diencephalic centers in emotional responses of animals it became necessary to devise some technique for destroying these deeper nuclei of the brain without releasing them from the restraining influence of the higher cortical centers. This meant that the destruction of the intervening nervous tissue had to be held at a minimum. After considerable experimentation a technique has been devised utilizing high frequency electric currents, which accomplishes well-defined destruction in internal cell masses and which enables the operator to exercise a very precise control over the locus and the amount of the tissue affected.

The high frequency current is generated by a shielded thermionic oscillator[1] which has an output of 50 watts at a frequency of 3×10^6 cycles per second. Most of this energy is dissipated in a voltage stabilizing circuit. A relatively small amount of the current is applied to an electrode, which is insulated except for one or two millimeters at the tip. This electrode produces negligible mechanical injury when it is inserted into the tissue because of its small diameter, which is approximately 0.3 mm, including the insulation. By using the proper duration and density of current, a definite globular region of thermally coagulated tissue surrounding the electrode tip may be produced. A large indifferent electrode is used to complete the circuit. The amount of tissue destroyed varies with the amount of uninsulated electrode surface, as well as the current density. A thermionic voltmeter across the active and indifferent electrodes has proven more useful in controlling the current than has direct measurement of the current flow. Shreds of tissue adhere to the electrode tip if the voltage is too high, which is of course objectionable in many cases. This usually may be prevented if the proper voltage-duration ratio is used.

In operating upon the deeper nuclei of the brain the first step is that of trephining the cranium. Following this the electrode is inserted with a goniometer-manipulator, accurately oriented with respect to the animal's brain by various landmarks on the skull. The manipulator is designed so that the electrode can be placed in any position and inserted at any angle desired. The animal's head is immobilized by means of suitable clamping devices. The precise adjustments of the goniometer for accomplishing destruction in any desired area are previously worked out from the stained sections of the brain of another animal. The proper voltage-duration ratio for producing a given amount of destruction must also be worked out previous to the operation.

To date, the method has been used only for producing internal lesions in the encephalon. It should, however, prove serviceable wherever controlled lesions in the deeper structures of the body are required. Because of the accurate control over the amount of destruction, the method can be used for making extremely minute lesions which are difficult of accomplishment by mechanical means.

CLARENCE W. BROWN
FRANKLIN M. HENRY
UNIVERSITY OF CALIFORNIA

[1] The writers wish to express their appreciation to the National Research Council for a grant-in-aid for constructing the high frequency unit.

A SIMPLE CALIBRATION METHOD

I HAVE devised a method for calibrating pipettes which is so simple that any technician who can perform a determination of uric acid in blood may use it. The method is believed to be original.

The example which follows is based on the uric acid determination, but other substances may be used.

The stock standard solution of Folin and Wu[1] is a 0.1 per cent. solution of uric acid, 0.020 cc of which contains 0.020 mg of the substance—the amount contained in 5 cc of the dilute standard.

To calibrate a capillary pipette to deliver, say, 20 cmm, it is necessary first to mark it approximately

[1] *Jour. Biol. Chem.*, 54: 153, 1922.

with a wax crayon. Then fill to the mark with the stock standard solution and discharge into a small volume of water in a test-tube. Draw up a little water and discharge this also into the test-tube. In another tube place 5 cc of the dilute standard solution. Make both tubes up to equal volumes with water and proceed with the determination in the usual way. With the standard set at 20 a reading at 20 would, of course, mean that the crayon mark is correct.

It is, of course, necessary that the 5 cc pipette be correct, as all capillaries will reproduce whatever error it may have.

The method may be employed to calibrate any size pipette by using solutions of appropriate concentration. The volume of a single drop also may be determined: a great convenience sometimes.

JOHN E. HEARN

FRENCH HOSPITAL, NEW YORK

SPECIAL ARTICLES

PREVENTION OF EXPERIMENTAL EQUINE ENCEPHALOMYELITIS IN GUINEA PIGS BY MEANS OF VIRUS ADSORBED ON ALUMINUM HYDROXIDE

RHOADS[1] reported the prevention of experimental poliomyelitis in monkeys by the use of virus adsorbed on aluminum hydroxide, Wilstaetter's Type C.[2]

In experiments with the virus of equine encephalomyelitis[3] an attempt was made to immunize guinea pigs against the experimental disease by means of the virus so adsorbed. It was found, however, that the adsorbent, when injected subcutaneously in amounts comparable to those previously employed, produced large, nodular masses which resolved with difficulty and often became inflammatory. Inasmuch as aluminum hydroxide prepared at pH 6.6 and sterilized by heat adsorbs as much as 99 per cent. of the virus from active material, the use of less than one twentieth of the amount of the colloid hitherto employed resulted in active immunization of the test animals. Moreover, the sites of injection showed only inconsiderable, localized indurations that disappeared within 5 or 6 weeks.

The source of virus was either the brain of guinea pigs which had succumbed to the experimental disease, or tissue cultures.[4] The latter were found to be more desirable, since less protein is present and hence less adsorbent is required. Another advantage is that in tissue-culture virus concomitant infectious agents can more easily be controlled.[5]

Guinea pigs received three subcutaneous injections of one cubic centimeter each, at 7-day intervals, of the adsorbed virus. The adsorption is of such a character that none of these animals revealed signs of infection during the period of immunization. On the tenth day after the third injection, they were shown to be resistant to an intracerebral inoculation of virulent guinea pig brain material in dilutions of 1:600 to 1:1600.[6] It should be emphasized that the virus was introduced directly into the brain in the test dose, which was lethal for control animals in dilutions of 10^{-5} or 10^{-6} when given subcutaneously or intracerebrally, respectively.

Thus far 40 guinea pigs have been inoculated with the aluminum hydroxide-virus material: 16 with the Western strain of tissue-culture virus, 10 with a mixture of Eastern and Western strains of similar material; 9 with the Eastern strain of guinea pig brain virus, and 5 with a mixture of Eastern and Western strains of the brain virus. None of these animals was affected after the intracerebral injection of the homologous strains as a test for resistance. On the other hand, all the 14 control, non-immunized guinea pigs died of experimental encephalomyelitis within from 72 to 96 hours after the test inoculation.

Investigations are now under way on the possible use of this method in preventing experimental encephalomyelitis of the monkey and the horse, the length of time the adsorbed virus retains its potency (thus far determined to be at least 10 weeks), and the duration of the resistance after the immunization.

HERALD R. COX
PETER K. OLITSKY

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK, N. Y.

[1] C. P. Rhoads, *Jour. Exp. Med.*, 53: 399, 1931.

[2] R. Wilstaetter and H. Kraut, *Ber. chem. Ges.*, 56: 149, 1923.

[3] We are indebted to Miss B. Howitt, of the University of California, for the Western, and to Dr. C. TenBroeck, of the Rockefeller Institute, for the Eastern strain of the virus.

[4] H. R. Cox, J. T. Syverton and P. K. Olitsky, *Proc. Soc. Exp. Biol. and Med.*, 30: 896, 1933; J. T. Syverton, H. R. Cox and P. K. Olitsky, SCIENCE, 78: 216, 1933.

[5] T. M. Rivers and S. M. Ward, *Jour. Exp. Med.*, 58: 635, 1933.

THE THERAPEUTIC BEHAVIOR OF LUCILIA SERICATA MEIG. LARVAE IN OSTEOMYELITIS WOUNDS

THE blowfly maggot (*Lucilia sericata* Meig.) removes by ingestion the acid-forming and bacterial-

[6] All operations on animals were performed with the aid of ether anesthesia.

growth-promoting necrotic tissue from an osteomyelitis wound by means of the macerating activities of the powerful mouth-hooks and predigestion, or liquefaction, by the tryptase present in the excreta, as shown by Hobson[1,2,3] and Mackerras and Freney[4] in experiments with maggots upon carrion. The action of this excreted tryptase, which arises in the mid-gut, is dependent upon an alkaline reaction which is imparted to the wound by ammonia in the feces and by calcium carbonate, which is continually exuded in small quantities through the body wall.[5] The removal of the necrotic tissue and the alkalization of the wound result in a reduction of the swelling of the soft tissue, with consequent increased drainage and decreased bone destruction, in protection to the tissue cells from autolysis stimulated by an acid condition and in retardation of bacterial growth. The calcium ions liberated from the exuded calcium carbonate stimulate phagocytosis.

The characteristic healthy granulation of wounds treated with blowfly larvae is, from experimental evidence,[5] apparently due to the alkalization of the wounds.

The increased rate of growth of larvae placed in wounds in which these organisms have been employed for some time and the occasionally high mortality of young larvae placed in such wounds are both due to ammoniation of the wounds by larval activity.

Bacteriological tests of the mid- and hind-guts of maggots previously fed upon *Staphylococcus aureus*, the most common etiologic agent of osteomyelitis, are consistently negative, but histological examinations of similar guts show undissoluted bacteria to be as numerous in the rectum as in the proventriculus. Hobson[1,3] has shown that the middle segment of the mid-gut of *L. sericata* larvae has a pH value of from 3.0 to 3.5. Exposure at 30° C., the apparent minimum temperature of an osteomyelitis wound, of growths of *S. aureus* to McIlvaine's Buffer Solutions ranging through pH values of 3.0, 3.2 and 3.5 demonstrated that marked mortality occurs at the highest pH and at a pH of 3.2 complete killing was effected well within the time limit during which the food is retained in the acid region of the mid-gut. Thus are many of the pathogenic organisms removed from the wound; however, not enough of them are ingested to make this the chief factor in securing propitious results.

It is believed that a considerable portion of the destructive leucocidin liberated by the bacteria is ingested by the maggots and probably rendered inert in the acid region of the intestines by means of the direct action of the acid or by virtue of its possession of an isoelectric point close to, or at, the point of concentration of the acid.

The writer succeeded in readily developing extensive myiases in guinea pigs and in one human with *L. sericata* larvae. It was demonstrated that these maggots will readily attack normal, healthy tissue if necrotic tissue is not present, and even if it is present but not immediately accessible. It was further demonstrated, however, that these organisms do prefer necrotic tissue, provided it is exposed to their action at the time of implantation into the wound. From these findings it becomes apparent that blowfly larvae are potentially dangerous in human wounds and must, therefore, be employed with care and skill.

Brumpt[6] has suggested that the larvae of the French and Chinese strains of this fly will attack normal tissue but the American strain will not. The writer has demonstrated such not to be the case by easily and repeatedly causing experimental myiases in guinea pigs, with no necrotic tissue present, with two different American strains.

Furthermore, the author caged seven sterile *L. sericata* larvae upon perfectly intact, healthy epidermis of his fore-arm which penetrated the skin and subcutaneous tissue to a depth of 3 mm in less than forty-eight hours.

M. A. STEWART

THE RICE INSTITUTE

THE NATIONAL ACADEMY OF SCIENCES. III

The unification of relativity theory and quantum theory: SIR ARTHUR STANLEY EDDINGTON. The basis of unification is that *a priori* probability in quantum theory furnishes the metric in relativity theory, the metrical tensor $g_{\mu\nu}$ being identified with the energy tensor of the *a priori* probability distribution of the N particles of the system. The wave equation for a particle refers to a system in which one particle has a modified momentum distribution and the remaining N–1 particles (which are averaged) have the *a priori* distribution. The double wave function of this system is in practise replaced by a simple wave function, the physical system of N–1 particles being replaced by an ideal comparison frame which is treated as definitely known instead of as a probability distribution. The condition that this substitution is valid gives a quadratic equation for the mass associated with the simple wave function, and the two roots are the masses of the proton and electron, respectively.

[1] Hobson, *Jour. Exp. Biol.*, 8: 109, 1931.
[2] Hobson, *Biochem. Jour.*, 25: 1458, 1931.
[3] Hobson, *Jour. Exp. Biol.*, 9: 359, 1932.
[4] Mackerras and Freney, *Jour. Exp. Biol.*, 10: 237, 1933.
[5] Stewart, *Surg. Gynec. and Obst.*, 58: 155, 1934.
[6] Brumpt, *Ann. de Parasit. Hum. et Comp.*, 11: 403, 1933.

The energies of the atomic linkages in the normal paraffin hydrocarbons: FREDERICK D. ROSSINI (introduced by W. W. Coblentz). The energy of dissociation at 0°K of gaseous normal C_nH_{2n+2} into gaseous carbon and hydrogen atoms is shown to be a linear function of n above, but not linear below, n = 6. The deviations from linearity for the latter are: methane, 4.81 ± 0.08; ethane, 1.59 ± 0.14; propane, 0.83 ± 0.19; normal butane, 0.46 ± 0.27; normal pentane, 0.13 ± 0.37, kilocalories per mole. The deviations can be explained by distinguishing different kinds of C–H and of C–C linkages in normal C_nH_{2n+2}. For the normal paraffin hydrocarbons, and for carbon and hydrogen atoms in the normal state, the energy evolved in the reaction $C\ (gas) + 2H\ (gas) + C_nH_{2n+2}\ (gas) = C_{n+1}H_{2n+4}\ (gas)$, for $n > 5$, is $-\Delta H^\circ_0 = (20.8 \pm 0.9) + D_{CO}$ kilocalories per mole; and any assignment of values for the energy of dissociation of CO, for the energy of excitation of the carbon atom to the ^5S state, and for the energies of the one C–C and two C–H linkages formed in the reaction must satisfy this relation.

A new conception of metallic oxide hydrosols: ARTHUR W. THOMAS (introduced by H. C. Sherman). It is proposed to regard the micelles in hydrosols of the metallic oxides as polynuclear complexes arising through the process of olation (Pfeiffer, Werner) of basic salts in solution. Such a conception of polyolated complexes accounts for the properties and behavior of these hydrosols, such as decrease in acidity upon treatment with neutral salts and the order of effectiveness of neutral salt anions in this respect, the presence of anionic radicals in the cationic micelle, increase in acidity of the hydrosol upon aging and the concomitant increase in the refractory nature of the micelle upon aging. It also provides for the application of the knowledge of crystalloid complex ions to colloidal complexes.

Thio sugars: P. A. LEVENE and ALBERT L. RAYMOND. The methylthio pentose which occurs as a nucleoside in yeast has not been extensively studied because of the scarcity of the material. An attempt has therefore been made to prepare synthetic thio sugars, with the immediate object of studying their properties and the hope, ultimately, of synthesizing the natural sugar. The methods that have been evolved for this purpose and the products which have been prepared are presented.

Neglected factors in the development of thermal springs: E. T. ALLEN. Hot springs due to the same fundamental causes develop, under the influence of secondary factors, into distinctive types. Limestone is such a factor. Springs associated with it deposit travertine. Without it they would develop into a different type. Thermal waters of almost identical character may, or may not, deposit travertine, according as they stand in still pools, flow over rough outlet beds, escape by smooth channels or by very short runs. Springs of two radically different types arise in basins where the water supply is of different magnitude, and the supply depends in turn on the topography. In hot areas small water-supplies develop into shallow bodies of hot ground water, where leaching of rock by sulfuric acid is the dominant alteration process. Large water-supplies descend to much greater depths, reaching and dissolving the less volatile magmatic emanations and chemical products formed at deeper levels, thus generating hot spring waters which leach the adjacent rock in quite a different way.

Supposed meteorite scars of South Carolina: DOUGLAS JOHNSON. Typical oval "bays" of the South Carolina coast have recently been examined to test the validity of the meteorite-scar and other theories of their origin. Evidence will be presented which seems definitely to negative the theory that they are meteorite scars, and to support the conclusion that they represent former lake basins surrounded by rims of wind-blown sand. The sand was derived from the sandy borders of the former lakes, and characteristic effects of wave erosion are still traceable in places, although the lakes are now for the most part filled with bog deposits, thickly overgrown with vegetation. The remarkable parallelism of the oval "bays," as well as the varying breadths of the surrounding rims, is believed to be controlled by the winds. The rims themselves do not appear to be the product of waves or water currents, nor does any change in the level of land or sea seem necessary to account for the phenomena observed.

Geomorphic researches in the Yellowstone Park and Big Horn Basins, Wyoming: DOUGLAS JOHNSON, ARTHUR HOWARD and J. H. MACKIN. In connection with the Yellowstone-Beartooth-Big Horn research project, supported by a grant, in part, from the Geological Society of America, geomorphic researches along two major lines were prosecuted during the past summer. With a view to unraveling the physical history of the Grand Canyon of the Yellowstone, Howard, with the collaboration of Field and Johnson, has investigated the partially consolidated sediments (early described by Holmes and later discussed by Field and Jones) found adhering to the canyon walls in places, and has sought to determine the conditions under which they may have accumulated. Damming of the canyon by lava flows, landslides and ice, with consequent temporary laking of the Yellowstone River, are among the hypotheses tested. It has been found (a) that much of the high-level basalt represented as "recent" on earlier geologic maps of the region, and appealed to as a possible source of damming, is older than the supposed Pliocene basalt found partially blocking the canyon in places; (b) that this supposedly recent basalt at one place underlies a rhyolite flow, which latter has been dissected by streams, and the stream channels subsequently filled by more recent basalt; (c) that the great age of the high-level basalts makes it doubtful whether they can be appealed to as a means of damming the river, to cause deposition of the sediments in question; (d) that more than one period of damming is suggested, in which the more recent basalt flows, landslides and glacial ice may all have played a rôle, the presence of all being indicated, but the fact of damming by each not yet being demonstrated. In the Big Horn region,

Mackin, with the collaboration of Johnson and aided by Lucke and others, and Bogert, aided by Wiringa, have made extended studies of the behavior of streams entering the arid basin from the bordering ranges. The evidence indicates (a) that the heavily laden streams have swung widely over the basin floor, carving rock fans and pediments by the process of lateral planation; (b) that partially completed pediments constitute a series of smoothly planed rock terraces, each terrace being covered with a veneer of gravel laid down by the laterally shifting stream which carved it; (c) that remnants of pediments largely destroyed by subsequent erosion constitute high-level mesas or table-lands, each similarly capped by gravels; (d) that study of the gravels enables one to determine what stream was responsible for the carving of each terrace or mesa; and (e) to trace a former course of the Shoshone River across a mesa top and through a gap in Pryor Mountains long since abandoned by that stream; (f) that the terraces and mesas are not to be regarded as peneplanes or partial peneplanes, and that they do not necessarily indicate either successive changes in the relative position of general base level, or successive local uplifts of the adjacent mountain ranges; but may record variations in the graded condition of streams due to climatic or other causes; and (g) that long-range correlations of these erosion surface remnants are of doubtful validity. New topographic maps of some of the forms studied have been prepared and will be placed on exhibition, together with other products of the investigation.

Time measurements of an ice readvance at Littleton, N. H.: RICHARD J. LOUGEE (introduced by Charles P. Berkey). The lower dam at fifteen-mile Falls on the Connecticut River in Littleton, N. H., lies within the belt of the Littleton-Bethlehem moraine. Near the site of the dam in 1921 Antevs measured two varved clay sections a mile apart. The bottom varves of each rested on till, but the lowest varve of the section nearest the dam was about 280 years younger than the bottom varve of the other exposure. Antevs concluded that the ice had readvanced over the dam site and finally retreated some 280 years after the first uncovering. During construction on the dam site in 1930 Mr. I. B. Crosby noted two till sheets, each 30 to 80 feet thick, separated by a 30-foot bed of lacustrine sand. No varved clay was exposed between the sheets, but several hundred varves overlaid the upper sheet. In the summer of 1933 excavations were made near the diversion channel of the dam, and the writer observed 119 slightly contorted varves resting on 15 feet of till, which in turn lay on bed rock. Since the bottom varve is some 270 years older than the lowest varve on the upper till sheet, this clay must lie beneath the upper till. These observations confirm Antevs' conclusions and show that: (1) lake waters covered the dam site for 119 or more years after the first withdrawal of the ice; (2) readvancing ice overlay the site of the dam for 151 years and deposited the upper till sheet; and (3) some 270 years after the first retreat the ice finally withdrew and lacustrine conditions ensued for several hundred years.

The fauna of the White River Oligocene: W. B. SCOTT. Work on the great assemblage of mammals and reptiles which have been found in the Bad Lands of South Dakota, Nebraska and the adjoining states, must begin with Dr. Joseph Leidy's great monograph of 1869. Dr. Leidy was not himself a collector, but was dependent for his material upon the fossils sent him by others, especially by Dr. Hayden, who enjoyed the fortunate reputation among the Indians of being mad and therefore inviolable. Leidy's warning to paleontologists not to expect "novelties" for half a century to come has been rendered nugatory by the great advance in the art of collecting, an art which was developed by the men who worked for Professor Cope and Professor Marsh, above all by the late Messrs. Hatcher and Wortman, not to mention living men. In Leidy's time collecting consisted of picking up such fossils as had weathered out of the matrix and were lying on the surface, and erosion in those arid regions is very slow. Twenty or more museums have undertaken the work of collecting in the White River area, for in none of the American Tertiary formations is there such a wealth of beautifully preserved material; and in the list prepared for me by my colleague, Professor W. J. Sinclair, there are 94 genera and 339 species of mammals already named, to say nothing of the many tortoises and lizards. No doubt, the number of species must be largely reduced, but the genera will probably remain as numerous as at present.

The seeds of Supaia, a Permian Pteridosperm: DAVID WHITE. Several seeds apparently attached at the bases of as many pinnules of a fern-like plant, from the Permian Hermit shale in the Grand Canyon, Arizona, described by the author as a new genus, *Supaia*, could not be proved beyond question to be in organic union with the fronds on account of the gritty nature of the matrix and the complete absence of the plant substance, due to oxidation in the arid climate of the region and time. A fragment similarly oxidized, of *Supaia*, recently found in the Supai formation of the Apache Indian Reservation, Arizona, reveals the impressons of small cordiform platyspermic, winged seeds, completely agreeing with those from the Grand Canyon, each attached by a pedicel, about 4 millimeters long, to the rachis at the base of a pinnule. Not only is *Supaia* thus conclusively proved to belong to the Pteridosperms, of which it is the seventh form-genus in the Permo-Carboniferous to yield definitely correlated seeds, but it becomes most probable that the *Cyclocarpon*-like seed described as apparently attached pedicellately to a frond from the Grand Canyon tentatively referred to *Brongniartites*, a genus very close to *Supaia* and regarded as Pteridospermic, is in place of growth and a Pteridosperm.

(*To be concluded*)

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